

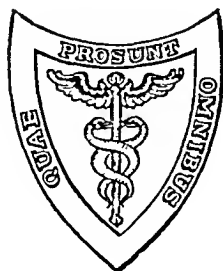
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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

JULY, 1937

ORIGINAL ARTICLES.

INTENSIVE COLLAPSE THERAPY IN PULMONARY
TUBERCULOSIS.

II. A STUDY OF THE INDICATIONS AND USE OF VARIOUS OPERATIVE PROCEDURES IN A GROUP OF 1124 PATIENTS.

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THE history of tuberculosis almost automatically divides itself into three phases, the last two of which have been initiated by revolutionary changes in therapeutic methods. The first phase was centuries long, characterized by a sense of futility and resignation toward the disease, and so far as treatment is concerned, chiefly by the mere palliative management of the outstanding symptoms. It almost abruptly merged, only a few decades ago, into the "rest-cure" conception of management. In its turn this second phase, by virtue of accumulated knowledge concerning the pathology and behavior of the disease under such a regimen, provides an important background and indispensable working adjunct for the therapeutic revolution that has within comparatively recent years initiated the third phase, namely the development of the various methods of thoracic surgery. We except pneumothorax therapy from this latter classification, since it is not strictly a surgical development. However, this by no means minimizes its importance, since it has been a concomitant of both the second and third phase of tuberculosis progress, and its influence on the development of the later purely surgical methods is universally recognized. Pneumothorax remains today probably the most important single therapeutic measure available to us.

The evolution of collapse therapy still progresses, not only in the refinements of the various methods employed, but also in the continually widening concept by phthisiotherapists of the possibilities that lie in the extended clinical use of these procedures. This radical change in the perception of the possibilities of treatment, encouraged by the excellent final results of treatment being reported, finds expression in the present attitude toward bilateral disease, toward which we have lost most of our recent pessimism. Bilateral cavities are today attacked with almost as much confidence as marked the application of pneumothorax therapy to unilateral disease only a few years ago.

In a recent paper² in this journal we gave in some detail the final results of treatment of a series of 1124 patients with the adult type of pulmonary tuberculosis consecutively admitted to this sanatorium between June 1, 1930, and June 30, 1931, of whom nearly 80% had one or more collapse therapy operations. The results provided an excellent justification of this apparently high percentage use of such therapy: Of 823 discharged patients, the tuberculosis of 47.3% of the entire group and 55.4% of those surgically treated, became arrested or apparently arrested; favorable results (improved to arrested), were 67.1% and 77.8% respectively; in the entire group of 1124 patients (78.8% of whom had surgical treatment), cavity closure was effected in 61.2% of all cases with cavity, and in 71.5% of the surgically treated cavity cases; sputum conversion was effected in 61.9% of all patients with positive sputum, and in 71.8% of those surgically treated.

An adequate analysis of any therapeutic program is necessary for its proper evaluation and an appreciation of the results of treatment. The tables presented in this article attempt to give a somewhat detailed analysis of the indications and actual use of the various methods of collapse therapy employed in this large series of patients. These statistics are closely identified, classification for classification, with the results of treatment previously reported, and, except for lack of space, would properly have been published in the same article. A comparison of the tables in the two articles at once makes apparent the amount and character of the collapse therapy that was responsible for certain results in corresponding small group-subdivisions of the entire series of patients.

Interpretation of Tables. Each of the first three tables, similarly arranged, gives, in the first two columns under each diagnostic classification, the number of patients under treatment for more than 6 months and for less than 6 months, respectively, who received a certain operation or combination of operations (see operation code under Table 1). The fifth and sixth columns in the same section indicate the total number of operations performed for that group of patients. Here the duplication of operations becomes evident. For example, in the third line of Table 1, fourth section, it will be seen that 224 phrenic operations were performed on 182 patients who were treated for more than 6 months, and that these patients also

received pneumothorax therapy, 10 having had bilateral pneumothorax. It is also seen that one patient received a scalenectomy in addition to pneumothorax and phrenic surgery, and that another had a multiple intercostal neurectomy operation. It was necessary, throughout the tables, to insert in this way the code for scalenectomy and intercostal neurectomy, since the addition of sections to the tables for these operations in their proper combinations with the five more important procedures would have made the tables impossibly cumbersome. For the same reason oleothorax is considered separately in the text. However, in order to avoid confusion, percentage figures in Columns 3 and 4 are based strictly upon combination of the five procedures at the left of the table. The inserted operations are so few in number, relatively, as to cause no important change in the percentages. Column 3 in the same section of Table 1 indicates that 32.6% of the 595 surgically treated patients received the combination of artificial pneumothorax and phrenic surgery, and Column 4 indicates that 23.6% of the 823 combined surgically and non-surgically treated patients received these two procedures.

Table 4, in summary, presents a percentage compilation of the various individual procedures, and indicates their relative importance in the therapeutic program. No comparison between the proportions of collapse therapy for male or female patients has been made, nor has any study been made of the application of collapse therapy by age groups, although such figures would be interesting. Approximately 12% of the discharged patients were more than 40 years old, and less than 4% were more than 50.

Collapse Therapy in Discharged Patient Group (Table 1). The subheadings of this table indicate the percentage of the minimal, moderately advanced and far advanced patients who had collapse therapy before discharge. The corresponding results of this treatment, as indicated by the condition of these 595 patients at the time of discharge, may be obtained by referring to Section 1 of Table 1 of the previous report.³ It is interesting to note that, of the 39 minimal cases which received collapse therapy, none received pneumothorax alone, although 36 had phrenic surgery alone, and 3 had the two procedures combined. It is quite apparent that more than half of the 90 minimal patients discharged were thought to be in such satisfactory control of their lesion as not to require collapse therapy during their hospital stay and, furthermore, that phrenic surgery and pneumothorax for the remainder apparently forestalled the development of complications that might have required more risky surgical methods. Since 1934, however, nearly 90% of the minimal cases admitted have received collapse therapy, in contrast with the 43.4% of this report.

It will be noted that, of the 215 discharged moderately advanced cases which received collapse therapy in some form, phrenic surgery was apparently the only treatment considered necessary for 53.9%, with the exception that one of the 116 patients comprising this therapy group had a multiple intercostal neurectomy, and 2 others a scalenectomy. Pneumothorax alone, and combined pneumothorax and phrenic surgery, were used for 76 patients, leaving only 23 patients, or 10.8% of the 215 surgically treated moderately advanced cases, for whom more advanced surgery was prescribed.

Extrapl. pn lysis	-	-	-	-	-	-	-	2	-	0.9	0.8	2EP	-	3	-	0.9	0.7	5EP	-	5	-	0.8	0.6	7EP		
Pneumothorax Thoracoplasty	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	0.6	0.4	2Px 7Th	-	2	-	0.3	0.2	2Px 7Th		
Pneumothorax Phrenic surgery Thoracoplasty	-	-	-	-	-	1	-	-	-	1.9	1.5	4Px 4Ph 12Th	-	27	-	7.9	5.7	1Sc 1IN *2Px 25Px 30Ph 82Th	-	31	-	5.2	3.8	1Sc 1IN *2Px 29Px 34Ph 91Th		
Pneumothorax Phrenic surgery Intrapl. pn lysis Thoracoplasty	-	-	-	-	-	-	-	-	-	-	-	-	-	3	-	0.9	0.7	3Px 4Ph 4IP 11P 17Th	-	3	-	0.5	0.1	3Px 4Ph 4IP 17Th		
Pneumothorax Phrenic surgery Extrapl. pn lysis Thoracoplasty	-	-	-	-	-	-	-	-	-	-	-	-	-	5	-	1.5	1.1	*1Px 1Px 7Ph 7EP 7Th	-	5	-	0.8	0.6	*1Px 4Px 7Ph 7EP 7Th		
Phrenic surgery Extrapl. pn lysis Thoracoplasty	-	-	-	-	-	-	-	-	-	-	-	-	-	4	-	1.2	0.9	4Ph 4EP 9Th	-	4	-	0.7	0.5	4Ph 4EP 9Th		
Phrenic surgery Thoracoplasty	-	-	-	-	-	-	-	-	2	-	0.9	0.8	2Sc 2Ph 7Th	-	11	3	1.1	3.0	2IN 13Ph 29Th	3Ph 6Th	13	3	2.7	1.9	2Sc 2IN 15Ph 36Th	
Extrapl. pn lysis Thoracoplasty	-	-	-	-	-	-	-	-	1	-	0.5	0.4	1EP 3Th	-	-	-	-	-	-	1	-	0.2	0.1	1EP 3Th		
Thoracoplasty	-	-	-	-	-	-	-	-	1	-	0.5	0.4	2Th	-	1	1	0.6	0.4	3Th	3Th	2	1	0.5	0.4	5Th	
Totals	35	4	100	0	43	4	3Px 4Ph 40Ph	191	24	100	0	81	8	100	0	311	30	293Px 200Ph 31IP 32EP 154Th	*1Px 22Px 16Ph 4IP 9Th	537	58	100	0	72	3	17Sc *1Px *26Px 287Px 561Ph 37IP 43EP 178Th

In Columns 5 and 6 of each section, the code letters are interpreted as follows. Px = Pneumothorax. Ph = Phrenic Surgery. IP = Intrapleural Pneumolysis. EP = Extrapleural Pneumolysis. Th = Thoracoplasty. Se = Sclerectomy, IN = Intercoastal Neurotomy.

* Wherever used in the table indicates bilateral pneumothorax.

† Intercoastal Neurotomy (IN) and Sclerectomy (Se) are treated as inserts in Columns 5 and 6 of each section and are not classified at the left of the table, and the number preceding the code letters indicates the number of patients rather than the number of operations.

These figures also apparently attest to the value of phrenic surgery and artificial pneumothorax, if performed without delay after the admission of the patient, in forestalling further development of the disease. The 23 patients who required more extensive surgery are divided (Section 2, Table 1) into 9 different groups according to the operative procedures performed singly or in sequence. Phrenic surgery was combined with extrapleural pneumonolysis with paraffin plumbage for 3 of the 23 (1 patient also had a scalenectomy). Thoracoplasty operations were performed for 8 of the 23 patients, in 1 instance alone, and for 7 patients combined with one or more other procedures. Another rather significant fact is that, while 87 of these 215 patients had pneumothorax therapy, only 6 required the intrapleural division of adhesions which prevented an effective collapse of the lung. As this operation was necessary in less than 7% of the moderately advanced pneumothorax cases, while it was necessary in 12.4% of the far advanced cases with pneumothorax, it is quite apparent that these figures corroborate the general belief that the development of pleural symphysis tends to parallel the progressive development of the pulmonary disease. Further evidence is furnished by the fact that in the moderately advanced group only 16.3% of attempted pneumothoraces resulted in failure to induce a satisfactory collapse, as compared with 27.3% in the far advanced group.

As compared with the former group, a marked change is noted in the character of the treatment given to the 341 far advanced surgically treated cases. Only 17%, as compared with 53.9% for the moderately advanced group, were subjected to phrenic surgery alone (1 case also received intercostal neurectomy). Pneumothorax alone, and combined pneumothorax and phrenic surgery, were prescribed for 53% of the group, as compared with 35.3% of the moderately advanced group. This leaves 102 patients, or 30%, as compared with 10.8%, for whom more drastic surgical measures were found necessary to supplement these two procedures. Approximately 56% of these had thoracoplasty operations, alone in 2 instances, and in combination with one or more other procedures in 55 patients. Extrapleural paraffin plumbage was resorted to in approximately one-fourth (25.5%) of this major-surgery group of 102. In 3 instances this was the only operation, and in 9 instances it was performed in conjunction with thoracoplastic surgery; in this connection plumbage and thoracoplasty were either used on opposite sides, or occasionally the thoracoplasty was a supplementary operation on the same side when plumbage failed to close completely the pulmonary cavity.

(It should be explained that, where major surgery such as thoracoplasty is the only procedure listed, pneumothorax therapy has almost invariably been unsuccessfully attempted. Statistics for these failures are not tabulated.)

The combined figures for the entire group of 823 discharged patients (Section 4, Table 1) would seem to indicate that in the average large group of patients subjected to intensive collapse therapy, and for whom treatment has been completed, approximately one-fourth of the group will require nothing more than phrenic surgery; that artificial pneumothorax will have been used, for the most part in conjunction with other procedures, for more than 40% of all patients (being indicated, if unsuccessful attempts to induce pneumothorax are included, in approximately 50% of patients); that extrapleural thoracoplasty will be indicated in about 8% of all patients; and that approximately 15% of such an average group of patients will require major thoracic surgery.

Collapse Therapy in Resident-patient Group (Table 2). The reason for the extremely high percentage of collapse therapy in this group (291 patients, or 96.7%), is explained by the fact that, while no patients were included in this study who were admitted after June 30, 1934, the statistics for resident patients were obtained as of January 1, 1935. Therefore all these patients had at least 6 months' treatment. All patients admitted up to June 30, 1934, who had less than 6 months' treatment, automatically fall into the discharged group (Table 1), including all patients discharged during the 6 months previous to January 1, 1935.

From this figure (96.7%) we can therefore draw a significant inference. Collapse therapy is either immediately or eventually indicated for practically 100% of all patients who remain in a sanatorium for at least 6 months. The small group of slightly more than 3% who were not under such therapy includes 2 minimal cases, and 4 far advanced terminal cases who lingered beyond expectation.

For this reason, a comparison of the use of surgical methods in this group with those in the discharge group would not be equitable. The resident group would naturally include a much larger proportion of the more unstable lesions. This is apparently shown in Sections 1 and 2 of Table 2. Nearly 31% of the 13 minimal cases under collapse therapy required pneumothorax as an adjunct to phrenic surgery, as compared with less than 8% of the 39 discharged minimal cases. In the moderately advanced resident group, 29.7% of the surgically treated patients required more operative aid than pneumothorax or phrenic surgery could give them, as compared with 10.8% in the discharge group. The corresponding figures for the far advanced cases requiring more advanced surgery are 44.5% as compared with 30%. It will be noted that in the resident group thoracoplasty plays a much more important part (Section 4, Table 2). Nearly 18% of the 291 surgically treated resident patients required thoracoplasty, as compared with 11% of the discharged patients. It must also be remembered that this resident group will probably require more surgery before discharge marks the end of treatment.

TABLE 2. —CLASSIFICATION OF VARIOUS OPERATIONS USED FOR 291 RESIDENT PATIENTS.

	Minimal (13 of 15).			Moderately advanced (8% of 162).			Far advanced (18% of 184).			Combined (291 of 391).		
	Cases.	Percent of Total.	Percent of 1-182.	Cases.	Percent of Total.	Percent of 1-162.	Cases.	Percent of Total.	Percent of 1-184.	Cases.	Percent of Total.	Percent of 1-391.
Pneumothorax	—	—	—	12	12.2	11.8	39Px	15	5.3	52Px	27	9.3
Phrenic surgery	0	0.0	0.0	17Ph	7.0	2.6	11N	22	12.2	51N	61	21.0
Pneumothorax Phrenic surgery	4	3.1	2.7	41Ph	27	27.5	40Ph	63	35.0	81Ph	94	32.3
Pneumothorax Intrapleural pnylisis	—	—	—	—	—	—	—	—	—	—	—	—
Pneumothorax Intrapleural pnylisis Phrenic surgery	—	—	—	8	8.2	7.9	16Ph	21	11.6	24Ph	29	10.0
Pneumothorax Phrenic surgery	—	—	—	—	—	—	—	—	—	—	—	—
Pneumothorax Extrapleural pnylisis	—	—	—	3	3.1	2.9	3Ph	2	1.1	6Ph	5	1.7
Pneumothorax Phrenic surgery Intrapleural pnylisis Extrapleural pnylisis	—	—	—	—	—	—	—	—	—	—	—	—
Phrenic surgery Extrapleural pnylisis	—	—	—	3	3.1	2.9	3Ph	8	4.4	11Ph	11	3.8
Extrapleural pnylisis	—	—	—	1	1.0	1.0	1EP	—	—	—	1	0.3
Pneumothorax Thoracoplasty	—	—	—	—	—	—	3	1.7	1.6	3Ph	3	1.0
Pneumothorax Phrenic surgery Thoracoplasty	—	—	—	6	6.1	5.9	13Ph	21	13.3	18Ph	29	10.3
Pneumothorax Intrapleural pnylisis Thoracoplasty	—	—	—	—	—	—	—	—	—	—	—	—
Phrenic surgery Extrapleural pnylisis Thoracoplasty	—	—	—	—	—	—	2	1.1	1.1	2Ph	2	0.7
Phrenic surgery Thoracoplasty	—	—	—	3	3.1	2.9	3Ph	7	3.9	10Ph	10	3.5
Thoracoplasty	—	—	—	3	3.1	2.9	7Th	1	0.6	4Th	4	1.4
Totals	13	100.0	86.7	98	100.0	96.1	189	100.0	97.8	291	100.0	96.7

In Column 4 of each section, the code letters are interpreted as follows: Px = Pneumothorax, Ph = Phrenic surgery, IP = Intrapleural pneumonolysis, EP = Extrapleural pneumonolysis, Th = Thoracoplasty, Sc = Scalenectomy, IN = Intercostal neurectomy.

* Wherever used in the table indicates bilateral pneumothorax.
† Intercostal neurectomy (IN) and Scalenectomy (Sc) are treated as inserts in Column 4 of each section and are not classified at the left of the table, and the number preceding the code letters indicates the number of patients rather than the number of operations.

Collapse Therapy in the Entire Group of 1124 (Table 3). Most of the important points covered in the previous discussion apply here, with less change than is noted in comparison between Tables 1 and 2. However, we think it is important to emphasize certain points with exact percentage figures because the statistics in Table 3 are those detailing the treatment given a complete consecutively admitted patient group.

Apparently phrenic surgery (not necessarily permanent paralysis) is all that is necessary for seven-eighths (86.6%, Section 1) of the surgically treated minimal cases admitted to a sanatorium. In our complete study group, not one minimal case required anything other than phrenic surgery or pneumothorax. Since these measures were prescribed whenever there was the least roentgenologic or symptomatic evidence of active disease, we regard these figures (Section 1, Table 3) as proof of the value of such a treatment policy, in forestalling possible unfavorable developments. Incidentally, none of these patients died, in 72.2% the disease was arrested or apparently arrested, and the remainder were either discharged against advice or were permitted to go home because their excellent condition did not justify keeping them long enough to qualify under the National Tuberculosis Association standards for "apparent arrest."

Of the entire number of surgically treated patients (886, or 78.8% of the whole), pneumothorax was the only treatment used for 10.5%, phrenic surgery alone for 30.6%, and the combined procedures for 32.5%. There were, however, 10 of the phrenic surgery group of 271, and 6 of the combined pneumothorax and phrenic surgery group of 288 who had, in addition to these procedures, a scalenicctomy or multiple intercostal neurectomy. A total, therefore, of 250 patients (28.2% of the surgical group) required major surgery.

Extrapleural thoracoplasty, either alone (7 cases) or in various combinations with other procedures, was performed for 116 of these patients; this represents 46.4% of the major surgery group, 13.1% of the entire surgical group, and 10.3% of the entire series of patients. Extrapleural pneumonolysis with plombage was performed alone in 6 of this major surgery group, and with other procedures in a total of 56 patients, which represents 5% of the entire series, and 22.4% of the major surgery group. The intrapleural division of adhesions for unsatisfactory pneumothorax collapse was necessary in 80 patients, representing 32% of the major surgery group, 9% of the entire surgical group, and 7.1% of all patients studied.

Considering the whole group of 1124 patients, another significant fact is obvious from a study of Table 3 (Column 4, Section 4). Only one-twelfth (8.3%) of all patients had pneumothorax therapy alone. Therefore approximately 70% of all the patients admitted to the sanatorium had one or more actual surgical operations other than

Extrapl. pn'lysis	-	-	-	-	-	-	-	-	-	-	-	-	3EP	-	-	3	-	0.6	0.5	5EP	-	6	-	0.7	0.5	8EP	-
Pneumothorax Thoracoplasty	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	-	1.0	0.8	5Px 17Th	-	5	-	0.6	0.5	5Px 17Th	-
Pneumothorax Phrenic surgery Thoracoplasty	-	-	-	-	-	-	-	-	-	10	-	-	15Se *1Px 9Px 12Ph 30Th	-	-	51	-	9.8	7.8	3Se 2IN *8Px 43Px 55Ph 159Th	-	61	-	6.9	5.4	4Se 2IN *9Px 52Px 67Ph 189Th	-
Pneumothorax Intrapl. pn'lysis Thoracoplasty	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	0.2	0.2	*1Px 2IP 5Th	-	1	-	0.1	0.1	*1Px 2IP 5Th	-
Pneumothorax Phrenic surgery Intrapl. pn'lysis Thoracoplasty	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	-	0.8	0.6	4Px 5Ph 5IP 22Th	-	4	-	0.5	0.4	4Px 5Ph 5IP 22Th	-
Pneumothorax Phrenic surgery Extrapl. pn'lysis Thoracoplasty	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	-	1.0	0.8	*1Px 4Px 7Ph 7EP 7Th	-	5	-	0.6	0.5	*1Px 4Px 7Ph 7EP 7Th	-
Phrenic surgery Extrapl. pn'lysis Thoracoplasty	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	6	-	1.1	0.9	6Ph 6EP 14Th	-	6	-	0.7	0.5	6Ph 6EP 14Th	-
Phrenic surgery Thoracoplasty	-	-	-	-	-	-	-	-	-	5	-	-	2Se 1IN 5Ph 16Th	-	-	18	3	4.0	3.2	2IN 22Ph 63Th	-	23	3	2.9	2.3	2Se 3IN 27Ph 70Th 3Ph 6Th	3Ph 6Th
Extrapl. pn'lysis Thoracoplasty	-	-	-	-	-	-	-	-	-	1	-	-	1EP 3Th	-	-	-	-	-	-	-	-	1	-	0.1	0.1	1EP 3Th	-
Thoracoplasty	-	-	-	-	-	-	-	-	-	4	-	-	9Th	-	-	2	1	0.6	0.5	7Th	-	6	1	0.8	0.6	16Th	3Th
Totals	48	4	100.0	49.5	7Px 70Ph	4Ph	289	24	100.0	85.8	100.0	30	17Se 14IN *10Px 131Px 335Ph 16IP 20EP 58Th	12Se 4Px 25Ph 1EP	491	30	100.0	79.7	11Se 11IN *1Px 22Px 16Ph 4IP 9Th	11Se 11IN *1Px 22Px 16Ph 4IP 9Th	828	58	100.0	78.8	118Se *15IN *84Px 43IPx 882Ph 88IP 67EP 352Th	12Se *1Px 26Px 45Ph 4IP 1EP 9Th	

In Columns 5 and 6 of each section, the code letters are interpreted as follows: Px = Pneumothorax, Ph = Phrenic surgery, IP = Intrapleural pneumonolysis, EP = Extrapleural pneumonolysis, Th = Thoracoplasty, Se = Scalenectomy, IN = Intercostal neurectomy.
 * Wherever used in the table indicates bilateral pneumothorax.
 † Intercostal neurectomy (IN) and Scalenectomy (Se) are treated as inserts in Columns 5 and 6 of each section and are not classified at the left of the table, and the number preceding the code letters indicates the number of patients rather than the number of operations.

pneumothorax, of whom 24.1% required nothing more than phrenic surgery. Selections from a group of well developed operative procedures seemed to fit the various treatment indications far better than pneumothorax alone. Exactly 40% of the patients, it will be noted, had these operations either as an adjunct to or in substitution for pneumothorax. Nevertheless, in 70% of the patients in this treatment group of 1124, it was considered either inexpedient or unnecessary to rely on pneumothorax alone, although pneumothorax has been the cardinal standby of comparatively recent years. These statistics provide unquestionable and convincing evidence of the extent to which the third phase of tuberculosis treatment has progressed beyond its initiatory stage.

Unfortunately, lack of space makes it impossible to include in the tables any statistics covering the bilateral or unilateral distribution of these surgical measures. The mass of detail would be too confusing. Some of this information, however, is given under the sections dealing with the individual operations.

Pneumothorax Therapy. In this and the following sections, no attempt is made to estimate the value of the individual collapse procedures in the determination of the final results of treatment. Certain information is of value, however, as indicating the extent of the use of bilateral collapse therapy in the whole program.

In the entire series, bilateral artificial pneumothorax was induced in 85 patients, representing approximately 8% of the whole group, nearly 10% of the surgically treated group, and nearly 16% of all pneumothorax patients. About 20% of those who received nothing but pneumothorax had both lungs collapsed by this method. As indicating the trend for unstable cases with bilateral collapse to accumulate and remain under treatment for much longer than average periods, the percentage of bilateral pneumothorax among all pneumothorax cases was 7.9 for the discharged group, and 28.7 for the resident patients. A reference to Tables 1 and 3 shows that only a negligible percentage of the moderately advanced patients in both groups had bilateral pneumothorax therapy.

Pneumothorax therapy, either unilateral or bilateral, was induced in 542 patients, representing 48.2% of the entire treatment group, and 61.2% of the collapse therapy group of 886 patients (Table 4). In the discharged group of 823, pneumothorax was induced in 3.4% of the minimal, 33.1% of the moderately advanced, and in 53.2% of the far advanced cases, or 41.3% of all discharged patients. Corresponding figures for the classifications of the entire group of 1124 were 6.7%, 39.7% and 59.6%, or 48.2% of the total.

Pneumothorax therapy was later abandoned, for various reasons and at varying intervals, in many of the patients listed above, and in most such instances other surgical procedures were substituted. No attempt is made to classify or explain the limited treatment. No case appears in the statistics, however, in which a partially

effective pneumothorax was not continued for a period of at least one month.

TABLE 4.—USE OF VARIOUS OPERATIONS.

		Discharged patients (823).				Resident patients (301).				Entire group (1124).			
		Cases.	Per cent of 593 surgical.	Per cent of total.	Operations.	Cases.	Per cent of 291 surgical.	Per cent of total.	Operations.	Cases.	Per cent of 886 surgical.	Per cent of total.	Operations.
Pneumo- thorax	Unilateral	313	52.6	38.0	—	111	49.4	47.8	—	457	51.6	40.6	
	Bilateral	27	4.5	3.2	—	58	19.9	19.2	—	85	9.6	7.6	
Phrenic surgery	Unilateral	193	82.8	59.9	583	229	78.7	76.1	285	722	81.5	64.2	868
	Bilateral	10	1.6	1.2	23	15	5.1	4.9	36	25	2.8	2.2	59
Intrapl. Pn'lysis	Closed operation	33	5.5	4.0	35	28	9.6	9.3	30	61	6.8	5.4	65
	Open operation	2	0.3	0.2	2	10	3.4	3.3	11	12	1.1	1.1	13
	Closed and open operations	2	0.3	0.2	4	5	1.7	1.6	10	7	0.8	0.6	14
Extrapl. Pn'lysis	Paraffin Plomlage	Unilateral	31	5.2	3.7	36	16	5.4	5.3	17	5.3	4.2	53
		Bilateral	2	0.3	0.2	4	3	1.0	0.9	6	0.6	0.4	10
	Supraperiosteal bag	2	0.3	0.2	3	—	—	—	—	2	0.2	0.2	3
	Supraperiosteal muscle	1	0.2	0.1	1	1	0.3	0.3	1	2	0.2	0.2	2
Thoracoplasty		65	10.9	7.8	187	51	17.5	16.9	174	116	13.1	10.3	361
Multiple intercostal neurectomy		6	1.0	0.7	6	9	3.1	2.9	12	15	1.7	1.3	18
Scalenicectomy		9	1.5	1.0	9	11	3.7	3.6	11	20	2.3	1.8	20
Oleo-thorax		5	0.8	0.6	—	6	2.0	1.9	—	11	1.2	1.0	

Phrenic Surgery. It has for years been our policy to recommend, with few exceptions, a phrenemphraxis rather than avulsion or section, since we have found that occasionally a permanent paralysis of the diaphragm interferes seriously with later indications for more extensive surgery. Frequently patients have, during their course of treatment, several operations to paralyze temporarily the phrenic nerve for a period of approximately 6 months. Repeated operations inconvenience the patient very little. Occasionally a permanent paralysis is effected before discharge if there is doubt that the patient will take the proper care of himself after discharge, or if the patient is so situated as to make a periodic check of his condition

uncertain. In general, when the patient plans to report several times a year to a good phthisiotherapist, permanent paralysis is postponed indefinitely in all but a few instances. This policy is more rigidly carried out for the younger patients.

No attempt is made in the present study to classify the various indications for phrenic surgery. Its value as a lone procedure is illustrated in Tables 1 to 3, chiefly for the minimal and moderately advanced cases. A total of 747 of the 1124 patients had in all 927 operations, indicating that more than 150 operations were repeated (Table 4). Bilateral paralysis of the diaphragm was effected for 25 patients, who had a total of 59 operations. Very few of this latter group had a simultaneous bilateral paralysis, however. In this bilateral group 2 patients had 4 phrenic operations each, and 5 patients had 3 operations. Of the 722 patients who had unilateral phrenic surgery, 13 minimal, 64 moderately advanced and 52 far advanced cases (129 total) had one or more reoperations. Secondary paralysis was effected in 113 patients, tertiary in 15, and 1 patient had the same nerve paralyzed four times.

Phrenic surgery was used for 66.4% of all the patients treated, and for 84.3% of those surgically treated. As indicated before, it was the only procedure used in 24.1% of all patients, and in 30.6% of the surgically treated patients. Expressed in a more pertinent way, in 36.3% of all the phrenic surgery done no other procedure was added, while 63.7% of phrenic paralyses were performed in conjunction with other collapse measures, either on the same side, or as a lone procedure for the contralateral lung.

Intrapleural Pneumonolysis. The division of pleural adhesions under thoracoscopic control is an extremely valuable procedure in certain instances. The use of this operative procedure to convert and correct an ineffective and at times a dangerous partial pneumothorax collapse will not infrequently avert the necessity for a later thoracoplasty. While it is always advisable to secure the result with a closed operation, the open operation, after partial posterior resection of one rib, or an intercostal incision, is preferable to no attempt at all. The pneumothorax space is infrequently lost after the open operation, and our experience with fluid complications has not impaired our opinion of its value.

Of the 80 patients in this series who had adhesions divided, 7 had both the closed and open operations, and 12 had the open operation alone (usually after inspection had determined the closed operation inadvisable). Of patients with bilateral pneumothorax collapse, 5 had bilateral operations for division of adhesions, in one case both operations being of the open type. A total of 92 operations were performed on the 80 patients. This type of thoracic surgery was used for 9% of the 886 surgically treated patients, and 7.1% of all the patients in the study.

Extrapleural Pneumonolysis with Plombage. While the use of a foreign body to secure a mechanical partial collapse of the lung may not be sound in principle, it has been our experience that such procedure is occasionally justified when all other measures fail to close a cavity, and when there are contraindications to the use of thoracoplasty. In general, an apicolysis with paraffin plombage entails less surgical risk than thoracoplasty. Its indications are limited, however, by anatomic considerations. The results of this operative procedure at this Sanatorium⁴ have been such as to justify continued confidence in its importance.

The operation, including 4 suprapariosteal pneumonolyses, was used in this series for 5% of all patients, representing 6.3% of all surgically treated patients. A bilateral paraffin apicolysis was done in 5 cases, and of 47 unilateral operations, paraffin was used both anteriorly and posteriorly in 6 patients, making a total of 63 operations for 52 patients.

The posterior approach in general yields superior results to those secured by an anterior operation. In several patients small bits of paraffin were later expectorated, but no further untoward results were seen in these patients.

Suprapariosteal Pneumonolysis. The indications for this type of extrapleural pneumonolysis are extremely limited. The results secured elsewhere have not been such as to encourage its adoption to any but a strictly limited extent. In our series, 2 patients had an anterior operation with pectoral muscle plombage, and 2 had rubber bag plombage. The latter operation is apparently more effective posteriorly. However, with the use of the bag, periosteal bone regeneration may not occur.

Multiple Intercostal Neurectomy. The indications for this procedure have been limited to patients with unstable unilateral or bilateral disease, for whom other collapse measures have been ineffective, and for whom thoracoplasty is contraindicated at the time. In these cases the results of the operation, either attributed solely to this procedure, or to its effect in preparing the patient for later thoracoplasty, have been so satisfactory that we consider it indispensable in its very limited application. In our series, a total of 15 patients who had this operation represent 1.3% of the entire group, and 1.7% of the surgically treated group. Three cases only had the operation in two stages, and 3 far advanced and 1 moderately advanced case had scaleniectomy as an adjunct. At the present time the operation is being done routinely in two stages.

Scaleniectomy. The results of this operation have not been conclusive enough to justify much confidence in its value as an independent procedure. Our experience with it suggests that its chief value is as an adjunct to multiple intercostal neurectomy, in unstable cases in which the primary object is to secure as much immobility of the hemithorax as possible, in preparation for later

thoracoplasty. Table 4 shows its use in this series in 20 patients, 2.3% of the 886 who had collapse therapy. Table 3 indicates its combination with other operative procedures in 9 moderately advanced and 11 far advanced cases. In 4 cases it was used with multiple intercostal neurectomy, and in 2 cases with phrenic surgery alone.

Thoracoplasty. A total of 361 operations, an average of three stages per patient, were used for the 116 patients for whom this operation was eventually found necessary. At the time of admission, 20 patients had moderately advanced, and 96 far advanced tuberculosis. The incidence of thoracoplasty, therefore, was less than 6% in the 365 moderately advanced cases, and about 15% in 654 far advanced cases, or 10.3% of the entire group of 1121, which includes 105 minimal cases. Thoracoplasty was used for 13.1% of all patients who received any type of collapse therapy. Bilateral partial thoracoplasty was done for one patient only. Thoracoplasty has only rarely been used for moderately advanced tuberculosis, and the majority of the 20 patients mentioned above had considerable progression of the disease before operation.

We believe it to be significant that, in an institution in which the proportion of collapse therapy approximates 80%, and 60% of the cases are far advanced, thoracoplasty should be apparently indicated in only 10% of the patients. The explanation is undoubtedly that, through the judicious selection and use of eight other operative procedures, the necessity for an eventual thoracoplasty in many patients is avoided.

Oleothorax. This procedure, which does not appear in the tables, is of questionable value because of its very limited indications and the uncertain reaction to its use, especially in the presence of positive intrapleural pressures. The occasional nente response of the pleura to its injection and the ever present danger of fistula formation would seem usually to outweigh its possible value in maintaining collapse of the lung in the presence of an obliterative pleuritis, or for certain other indications. In our series, it has been employed in 11 patients, or slightly more than 1% of those who received collapse therapy.

Comment. Recently the development of thoracic surgery (including pneumothorax) was characterized in the literature as an important adjunct to the bed rest regimen. We take some exception to this phraseology. It is more accurate to say that collapse therapy and bed rest are absolutely interdependent upon one another, and that collapse therapy may no longer be considered as a mere adjunct to the more time-honored regimen. We are aware of the approximate fate of patients with pulmonary cavities afforded bed rest alone,¹ and we have statistical proof of the excellent results to be expected following the general use of collapse therapy in large groups of patients.^{2,3} There is no question about the indispensable value

of the bed rest regimen for consolidation of the gains effected by collapse therapy. However, those who temporize with bed rest until the need for thoracic surgery becomes urgent are incurring hazards and inviting unfavorable results that far outweigh any of the surgical risks attached to collapse therapy procedures.

It is interesting to note in the literature of recent years that many of those who at one time spoke of "The over-enthusiasm of the exponents of collapse therapy," now exhibit a notable reversal of opinion. Among increasing numbers thoracic surgery is being looked upon more and more as a conservative form of treatment. The more advanced operations, which were formerly considered to be radical surgery, are now accepted as almost entirely routine and unquestionably useful therapy.

With the exception of the following three categories of patients, we believe that practically all patients admitted to a sanatorium with the adult type of active pulmonary tuberculosis, should have collapse therapy: 1, Terminal cases; 2, those whose lesions are only questionably active (the majority of such patients actually do not require hospitalization); 3, those who refuse collapse therapy (the number should be negligible), or who leave the sanatorium for various reasons before collapse therapy is instituted. O'Brien states, "While we all recognize that patients with tuberculosis go through various phases, there is no phase of the disease in which collapse therapy is not indicated except in the terminal one when it is too late."

The paradoxical statement that the so-called radical surgical methods of yesterday have become the conservative treatment of today, applies as accurately to non-cavernous as to cavernous disease. Indeed, in the former group, collapse therapy has a definite prophylactic value in the prevention of cavity formation, and we do not acquiesce in the trite statement that the treatment of tuberculosis is largely the treatment of cavities. There is abundant evidence available that collapse therapy for minimal lesions, and for more extensive lesions without cavity, is productive of much better final results than when similar lesions are not so treated, largely because it tends to forestall the later development of cavities.

There have been many creditable attempts to correlate the expected clinical course of a patient with the pathology of the lesions as interpreted roentgenologically, and to make new classifications of tuberculosis from a prognostic standpoint. We believe that it is still unsafe to translate such classifications from a prognostic to a therapeutic significance. Because of the notorious inaccuracy of prognoses made during the early observation of tuberculous cases, it would seem ill-advised to attempt to classify patients into benign (requiring no collapse therapy) and malignant (requiring collapse therapy) groups. In the present state of our knowledge treatment cannot be predicated upon any of the known prognostic classifica-

tions, if it is to be prescribed within the limits of safety which we must accord the patient as his due. The general use of collapse therapy, with few contraindications, is conservative and should be the accepted procedure.

Summary. 1. Tabulated statistics are presented indicating the extent to which eight collapse therapy procedures, either singly or in various combinations, have been used in a series of 1124 patients.

2. There is an apparent indication that, in sanatoria having facilities available for thoracic surgery, and in which the admission of far advanced, moderately advanced and minimal cases approximates the ratio 6 : 3 : 1, the treatment expectations should be as follows:

(a) Artificial pneumothorax as an unaided procedure will suffice for only one-twelfth of all patients; singly or with other procedures it will be used for approximately 50% of all patients, or about 60% of all those surgically treated.

(b) Phrenic surgery as an unaided procedure will suffice for approximately one-fourth of all patients admitted; singly or with other procedures it will be used for approximately two-thirds of all patients, or about 85% of all those surgically treated. Phrenic operations will suffice for seven-eighths of the minimal, nearly half the moderately advanced, but only 15% of the far advanced cases.

(c) Phrenic surgery in conjunction with pneumothorax will suffice for approximately one-fourth of all patients, or about one-third of those surgically treated.

(d) Major thoracic surgery (excluding pneumothorax and phrenic surgery) will be necessary for approximately one-fifth of all the patients admitted, or for more than one-fourth of the collapse therapy group.

(e) Thoracoplasty should be required in no more than 10% of all patients, representing about one-eighth of the surgically treated group.

3. Bilateral collapse therapy was used for a total of 160 patients, 14.2% of the entire group, or 18.1% of those who received collapse therapy.

4. The intelligent selection and use of various collapse therapy measures should decrease the necessity for major thoracic surgery, and increase the favorable final results of treatment, in direct proportion to the intensity of such a program in the early stages of treatment.

The authors are indebted to Dr. John Alexander for valuable critical advice in the preparation of this article.

REFERENCES.

- (1.) Barnes, H. L., and Barnes, L. R. P.: *Am. Rev. Tuberc.*, 18, 412, 1928. (2.) Hanna, R. J.: *Am. J. Med. Sci.*, 191, 703, 1936. (3.) Leslie, G. L., and Anderson, R. S.: *Ibid.*, 193, 149, 1937. (4.) McIndoe, R. B., and Alexander, J.: *Am. Rev. Tuberc.*, 29, 270, 1934. (5.) O'Brien, E. J.: *J. Thorac. Surg.*, 5, 123, 1935.

DEATH FOLLOWING PHRENICECTOMY.

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THE lack of unfavorable incidents associated with avulsion of the phrenic nerve in the great majority of cases has caused most surgeons to consider the operation a minor one. This is reflected in the literature by such statements as: "The operation itself is attended with little or no risk to the patient" (Lemon⁷). "Mortality from phrenic exeresis is of course negligible" (O'Brien⁸). "The careful pulling of the nerve out of the chest cavity is not dangerous, as we may say after many hundreds of successful attempts" (Saucerbruch¹⁰). "Phrenicectomy is a minor operation" (Alexander¹), and many others. Hedblom⁴ recommended it as a test operation in detecting any tendency to respiratory incapacity, especially of the better lung, particularly in patients with low vitality capacity. The fact that the operation is considered such an uneventful one by the medical profession makes a catastrophe particularly embarrassing to explain to the family, who probably have been told about the simple procedure which only takes a few minutes under local anesthesia. Because of this prevailing view we have felt that it was advisable to collect the deaths due to phrenic surgery from the literature and at the same time report 2 additional deaths from our personal experience.

Berry² reviewed this subject in an excellent article in 1930. He collected from the literature a series of 4697 cases and found that there were 57 serious complications (1.2%) and 26 (0.55%) fatal cases. This mortality rate is an appreciable one for what is generally considered a minor procedure.

Wirth, Koeln and Jaski¹² reviewed a series of 600 cases listing the following complications: 11 cases of aspiration pneumonia, 6 cases of hemoptysis, 8 cases of dissemination of tuberculosis to the intestinal tract, 5 cases spread to the larynx, 12 cases with acute aggravation of the disease ending in death.

The causes of death in the collected cases are shown in the accompanying chart, a portion of them (14) being taken from Berry's² article. A summary of the causes of death shows that by far the largest number of deaths are due to spread and aggravation of the tuberculous disease. We, however, are particularly interested in the group of 8 cases who died a cardiorespiratory death, that is with dyspnea and cyanosis, pulmonary edema and tachycardia. Our 2 cases fall in this group and abstracts from clinical courses follow.

Case Reports. **Case 1.** The patient, a young white female, aged 33, whose past medical history was negative except for an attack of rheumatic fever at 16, was first seen in the outpatient department of the University Hospital on May 10, 1931, with a chief complaint of weakness and loss of weight. In 1932 she had begun to get short of breath while working. This was insidious in onset and was not precipitated by a respiratory infection. She continued to work although the dyspnea was marked and there was some edema of the ankles. A year later, May, 1933, she began to lose weight and felt tired. Rheumatic heart disease was first diagnosed at that time. She was advised to quit work and to stop climbing stairs. In January, 1934, she had a severe attack of bronchitis. With it there was cough and expectoration and the sputum was frequently blood-streaked. The cough and blood-streaked sputum persisted to the time of admission. She had lost 30 pounds in weight in the past year and was finally forced to stop work in March, 1934, because of weakness. Examination at that time showed a poorly nourished white female weighing 97 pounds. There were definite physical signs of tuberculosis in the upper third of the right lung (dullness to percussion, increased vocal resonance and posttussive râles). There was moderate cardiac enlargement and a systolic murmur was heard all over the precordium and transmitted to the axilla. The blood pressure was 110/80. There were no signs of cardiac decompensation. The sputum was repeatedly positive for tubercle bacilli.

Röntgen examination of the chest May 12, 1934, showed: Right lung infiltration with several moth-eaten cavities in the upper half. Left lung an increase in the trunk shadow to the apex but no definite infiltration. The heart is enlarged, 61% larger than predicted normal. The costophrenic angles are clear, trachea is in the midline.

This patient had failed to show any improvement on bed rest at home and was admitted to the hospital for some collapse measure. Röntgen examination of the chest on admission showed an increase of the disease in the right lung with more evidence of cavity formation. Pneumothorax was decided upon and 5 treatments were given. Following the second pneumothorax treatment there was an increase in the temperature range up to 102°. Since Röntgen examination of the chest showed only a slight collapse, phrenicectomy was decided upon and done under local anesthesia. The nerve was exposed without difficulty and crushed with a hemostat. She was returned to the ward in good condition, except for some dyspnea. Late in the afternoon of the day of operation she became slightly cyanosed and the pulse was rapid and weak. The cyanosis became worse and the patient was placed in an oxygen tent with only temporary improvement. The dyspnea and cyanosis became more marked, the pulse became weak and thready and the patient died 16 hours after operation. Autopsy permission was not granted. However, the entire clinical picture of the patient postoperatively justifies the conclusion that the death was due directly to cardiac failure. (From the service of Dr. E. L. Eliason.)

Case 2.—Mrs. J. P., admitted to Service No. 1 Tuberculosis Division, Philadelphia General Hospital, July 7, 1933, complaining of cough, expectoration, loss of weight and weakness for 2 years. Two years prior to admission the patient had been advised to stop work and to rest at home, but was unable to do this because of trying conditions at home. One year prior to admission her sputum was found to be positive for tubercle bacilli and for the past 6 months she has been resting in bed about 16 hours daily. In spite of her attempting to rest at home she grew progressively worse, the cough and sputum increased and she lost 40 pounds in weight. Past medical, family and social history was irrelevant. Physical examination showed: temperature 99.6°, pulse 100, blood pressure 112 systolic, 83 diastolic. In the right lung the percussion note, breath sounds and vocal resonance were appar-

ently normal. A few medium coarse râles were heard on inspiration after cough above the level of the second rib and fourth dorsal spine. In the left lung the percussion note was dull over the front and back, the breath sounds were bronchial and eavernous above the level of the third rib and seventh dorsal spine, with pectoriloquy in this same area and many posttussive râles over front and back. The trachea was displaced to the left. The heart was definitely displaced to the left, but was normal as far as physical examination could determine.

The Roentgen examination of the chest showed: "Right lung: small amount of infiltration in the upper third. Left lung: there is an extremely large cavity filling the entire lung field to the level of the third rib, with some infiltration below." The heart and mediastinum are displaced to the left. The sputum was repeatedly positive for tubercle bacilli.

This patient failed to show any improvement after several months of bed rest. The temperature range continued from 98° to 100°. After 3 months of bed rest there was no progression of disease in the right lung and a phrenic exeresis was decided upon, preliminary to thorocoplasty. On October 31, 1933, left phrenicectomy was done under local anesthesia. The nerve was exposed without difficulty. The nerve was freed, infiltrated with novocaine, sectioned and avulsed, 8 inches being removed. No accessory nerve was seen. The wound was closed in the usual manner and the patient returned to the ward in good condition. The day after operation slight dyspnea and cyanosis were noticed and following this the patient had attacks of dyspnea with increased cyanosis. There was no change in the physical signs in the right lung and there was some improvement in the temperature range. Fluoroscopic examination of the chest showed a rise in the left diaphragm of 5 to 6 cm. The attacks of dyspnea and cyanosis became more marked and more frequent and on the eighth day postoperative the patient died suddenly. Autopsy was performed, with the following findings: "Heart, weight 330 gm.; slightly larger than normal, with left ventricular hypertrophy. The heart cuts with decreased resistance, has a pale pink, cloudy appearance. Valves are grossly negative. Foramen ovale is partially opened. Left lung, weight 48 gm. The upper lobe is almost completely replaced by a cavity the size of a large fist with marked fibrosis. The cavity extends to the pleura and is lined by a thickened, grayish membrane. The lower lobe is compressed. Right lung, weight 530 gm. It pits on pressure and crepitates, except for tiny nodules throughout the upper portion. Upper lobe shows depressed scarred area of old, healed tuberculosis with a cavity 1.5 cm. in diameter underneath the pleura near the apex."

These 2 cases of death following phrenicectomy undoubtedly belong to the group described by some authors as dying from respiratory insufficiency, and by others as due to cardiac failure. The nearest approach to our cases was the case of Weber¹¹ who advanced the theory that the change of intrathoracic pressure with a shift of the mediastinal structures to the right (right phrenicectomy) was the cause of death in his case. He further brought forth the hypothesis that a left phrenic exeresis might have caused a return to normal relationship and saved the patient's life. In our first case this probably was a factor in addition to the preëxisting mitral lesion. His recommendation of doing a phrenicectomy on the contralateral side seems to be a radical form of therapy and most probably would not give the desired result but would further embarrass the cardiorespiratory system.

The 2 patients presented show evidence of cardiac involvement. The first had a definite mitral murmur and was known to have had rheumatic heart disease for several years prior to surgery. The second at autopsy showed a patent foramen ovale.

Paralysis of the diaphragm on one side frequently displaces the heart and changes its axis. This change increases the work of the heart and may be the precipitating factor in heart failure in cases with some pre-existing damage. Our first patient had an old rheumatic heart disease and in the second this change of position and axis of the heart might have caused the foramen ovale to become patent and in that way precipitate heart failure. These facts would seem to indicate that death was primarily due to a cardiac lesion rather than to a reduction in vital capacity. It must be remembered that reduction in vital capacity can be an important factor. One author states that the vital capacity is decreased as much as 36% by phrenicectomy, while another showed that it was reduced from 500 to 800 cc. In a normal individual the tidal air is only one-seventh of the vital capacity so that one would assume that it would have had to be much reduced pre-operatively for this reduction to have resulted fatally. Unfortunately, no pre-operative vital capacity studies were made in our patients. However in Case 2 there was no subjective dyspnea on moderate activity around the wards. Since these two fatalities, one of us was requested to do a phrenicectomy on a rather ill, advanced tuberculous patient in whom the vital capacity was only 1000 cc. This was thought to be sufficiently low to contraindicate phrenicectomy, as it would decrease the vital capacity to a point dangerously close to the normal tidal air of 500 cc.

The question naturally arises, what can one do to prevent similar catastrophes in the future? The collected mortality rate for this procedure is too high for a so-called simple operation. There is need for more rigid formulation of the indications and contraindications. From our experiences it would appear that any case with evidence of cardiac damage should be carefully observed for some time and a phrenic nerve operation done only after considering the risk and carefully weighing the advantages to be gained. The attitude that the patient is doomed unless something radical is done is not always justified. It may bring into disrepute an operation which is of definite value in properly selected cases. Epstein³ has proposed the following contraindications: 1. Definite, exudative type of disease. 2. Dissemination of the process in both lungs. 3. Hematogenous forms of tuberculosis. 4. Old cases of fibro-cavernous tuberculosis with extensive involvement of the contractility of the lung and secondary heart insufficiency. He speaks of the emphysematous heart and believes that in these chronic cases there is always the danger of right sided heart failure.

Hein⁶ suggests close observation of the patient during the period

between injection of local anesthesia and isolation of the nerve with the thought that if untoward symptoms arise (dyspnea, cyanosis and tachycardia) further surgery is contraindicated.

TABLE 1.—RECORDED FATALITIES AFTER PHRENICECTOMY.

Author and reference.	No. of cases.	Cause of death.	Time post-operative.
Berg, W.: <i>Deutsch. med. Wchnschr.</i> , 54, 874, 1928	1	Pulmonary embolism	6 hours.
Chandler, F. G.: <i>Brit. Med. J.</i> , 2, 605, 1928	1	Pulmonary edema	4 hours.
Curti, E.: <i>Policlinico (sez. prat.)</i> , 34, 1474, 1927	1	Dyspnea and tachycardia	10 days.
Dumarest and Berard, L.: <i>Rev. de la tubere.</i> , 9, 161, 1928	2	Contralateral spread of tuberculosis	?
Deist, H.: <i>Beitr. z. Klin. d. Tuberk.</i> , 63, 424, 1926	2	Pneumonia, pyopneumothorax	?
Hedblom, C. A.: <i>J. Mich. Med. Soc.</i> , 28, 535, 1929	1	Respiratory insufficiency	?
Kleinschmidt, P.: <i>Deutsch. med. Wchnschr.</i> , 53, 473, 1925	2	Hemorrhage caused by avulsion of nerve	?
Morone, G.: <i>Ann. ital. di chir.</i> , 4, 189, 1925	1	Pneumonia	9 days.
Schnippenkotter, W.: <i>Beitr. z. Klin. d. Tuberk.</i> , 65, 56, 1927	1	Spread of tuberculosis	?
Schenck, A.: <i>Ibid.</i> , 61, 552, 1925	1	Contralateral spread of tuberculosis	?
Sergent, E., Baumgartner, R., and Bordet, F.: <i>Bull. et mém. Soc. méd. d. hôp de Paris</i> , 50, 203, 1926	3	(1) Spontaneous pneumothorax and mediastinal emphysema; (2) on table of asphyxia; (3) hemoptysis	1 day.
Zadek, J., quoted by Epstein, D.	5	Pneumonia or spread of tuberculosis	?
Herben, G.: Personal communication to Berry	2	Mediastinal hemorrhage	?
Miller, J. A.: Personal communication to Berry	1	Pneumonia	Several weeks.
Thomopoulos, A., quoted by Berry: <i>Paris</i> , 1925	1	Hemorrhage from pericardiophrenic artery	24 hours.
Berry, F. B.: <i>Arch. Surg.</i> , 21, 1125, 1930	1	Pneumonia and edema	
Cassidy, M. A., and Lee, R. O.: <i>Brit. Med. J.</i> , 2, 684, 1933	1	Asphyxia	On table.
Caralps, M. H.: <i>Assn. Med. Barcelona</i> , 6, 100, 1930.	1		
Davidson, M., and Ledlie, R. C. B.: <i>Brit. J. Surg.</i> , 16, 198, 1928	1	Pneumonia spread	9 days.
Epstein, D.: <i>Tuberkulose</i> , 12, 203, 221, 1932	6	Tb. meningitis Dissemination of process Pneumonia Spread of tuberculosis	6 to 7 days. Not stated. 5 days. About 1 week.
		Spread to larynx On table, respiratory insufficiency	Not stated. On table.
Fernandez, G. A.: <i>Med. Ibera</i> , 1, 496, 1934	1	Hemoptysis	20 days.
Friedrich, S., quoted by Sauerbruch	1	Hemoptysis	Not stated.
Filotta, G.: <i>Riv. san. siciliana</i> , 21, 438, 1933	1	Hemoptysis	5 days.
Naegli, I.: <i>Zentralbl. f. Chir.</i> , 57, 2962, 1930	1	Hemoptysis	3 days.
Newing, W. J.: <i>Med. J. Australia</i> , 2, 224, 1934	2	Persistent vomiting	10 days.
O'Brien, E. J.: <i>J. Am. Med. Assn.</i> , 95, 650, 652, 1930	2	Hemoptysis	14 days.
Weber, J.: <i>Ibid.</i> , 103, 107, 1934	1	Pneumonia	Not stated.
Zadek, J., and Sonnenfeld, quoted by Epstein, D.	1	Respiratory failure	6 days.
	1	Hemoptysis	Not stated.
Cooper, D. A., and Erb, W.	2	Cardiac failure	16 hours.
		Cardiac failure	7 days.

Heymer^{6,8} suggests temporary paralysis by the injection of novocaine after which the respiratory function is tested by vital-capacity determination and by the length of time the patient can

voluntarily hold his breath (normal 50 to 70 seconds). Of these the first would appear to be too complicated, but the second is of practical value. They state that on the evidence of these tests they have refused to do one phrenicectomy.

TABLE 2.—SUMMARY OF 40 CASES OF DEATH

	Case
Asphyxia during apnoea	1
Cardiorespiratory failure	8
Hemorrhage (surgical)	5
Hemoptyses	7
Pneumonia	7
Pulmonary embolism	1
Pyopneumothorax	1
Pneumothorax and retraction and asphyxia	1
Spread of tuberculous process	13
Acute gastritis	1
Unknown	1
	40

In the Tuberculosis Division of the Philadelphia General Hospital one of us has recommended using a two-stage procedure in any questionable case. In the first instance, the nerve is exposed and injected with novocaine, any accessory nerves are cut and a black silk ligature is drawn around the nerve. The wound is then pulled together by adhesive and the patient observed from a few to 24 hours, when the operation is completed.

Conclusions.—1. Phrenicectomy is not a minor operation, but is attended by an appreciable mortality (0.5%).

2. Forty-four cases of death following phrenicectomy have been collected from the literature, to which 2 additional ones are added.

3. The contraindications to phrenicectomy are discussed. Any cardiac lesion should be considered a contraindication.

4. Pre-operative vital capacity studies should be made routinely.

5. At the time of operation the patient should be observed closely for signs of respiratory or circulatory embarrassment during the induction of the local anesthetic, using also the simple test of the patient's ability to hold his breath.

REFERENCES.

- (1.) Alexander, J.: *Surgery of Pulmonary Tuberculosis*. Philadelphia, Lea & Febiger, 1925.
- (2.) Berry, F. B.: *Arch. Surg.*, 21, 1125, 1930.
- (3.) Epstein, D.: *Tuberkulose*, 12, 203, 221, 1932.
- (4.) Hedblom, C. A.: *J. Michigan Med. Soc.*, 28, 535, 1929.
- (5.) Hein, J.: *Deutsch. med. Wchnschr.*, 52, 2028, 1932.
- (6.) Heymer, A.: *München. med. Wchnschr.*, 80, 1317, 1933.
- (7.) Lemon, W. S.: *Arch. Surg.*, 14, 315, 1927.
- (8.) Naegeli, T., and Heymer, A.: *Klin. Wchnschr.*, 12, 1565, 1933.
- (9.) O'Brien, E. J.: *J. Am. Med. Assn.*, 95, 650, 1930.
- (10.) Sauerbruch, F.: *Die Chirurgie der Brustorgane*, Berlin, Julius Springer, 1930.
- (11.) Weber, J.: *J. Am. Med. Assn.*, 103, 107, 1931.
- (12.) Wirth, Koehn and Jaski: Quoted by Epstein (Ref. 3).

CHRONIC MYELOGENOUS LEUKEMIA.

OBSERVATIONS BEFORE AND DURING REMISSIONS INDUCED BY SOLUTION OF POTASSIUM ARSENITE AND BY ROENTGEN THERAPY WITH PARTICULAR REFERENCE TO BONE MARROW.

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THE similarity of the therapeutic response of chronic myelogenous leukemia to Roentgen therapy and to a solution of potassium arsenite has been previously noted.^{1,3} Both result in temporary clinical remission, reduction in the number of total and immature white blood cells, improvement in the anemia and reduction in the elevated basal metabolic rate. A few isolated observations of the bone marrow after treatment suggest that there is a return to red marrow during remissions induced by both Roentgen therapy⁵ and solution of potassium arsenite.¹ Reports of detailed studies of the bone marrow before and after treatment have not been encountered in the literature.

This communication presents detailed observations of the peripheral blood, bone marrow, nitrogen balance and oxygen consumption in 2 patients with typical chronic myelogenous leukemia before and during satisfactory remissions induced by solution of potassium arsenite and by Roentgen therapy. The bone marrow findings are of particular interest.

Method. Each patient was admitted to the hospital for a period of observation. Daily white blood cell and differential counts, and frequent estimations of the red blood cells, hemoglobin and reticulocytes were made. The basal metabolism was determined at approximately weekly intervals. A diet of constant protein and caloric content was offered, and record was kept of rejected portions. Daily estimations of urinary nitrogen were made. Nitrogen excreted in the stools was determined in 6-day periods. Biopsy of sternal bone marrow was done in each instance before and after treatment. A small portion of the bone marrow obtained at biopsy was emulsified in serum and studied in supravital preparations and in fixed smears stained with Wright-Giemsa stain. Differential counts of 1000 cells were made in the fixed preparations. The remainder of the bone marrow sample was utilized for paraffin sections prepared in the usual manner and stained with hematoxylin-eosin and eosin-methylene blue.

Case Reports. CASE 1.—E. S., a single Italian girl of 23, had had poliomyelitis at the age of 4 with resultant deformities, including marked scoliosis, atrophy and shortening of the right leg and atrophy of the right arm and hand. She was first seen in this clinic in 1931 because of acute abdominal pain. At laparotomy she was found to have subacute salpingitis. Blood counts at this time were as follows: hemoglobin, 12.8 gm. per 100 cc.; red blood cells, 5,000,000; white blood cells, 11,700 per c.mm.

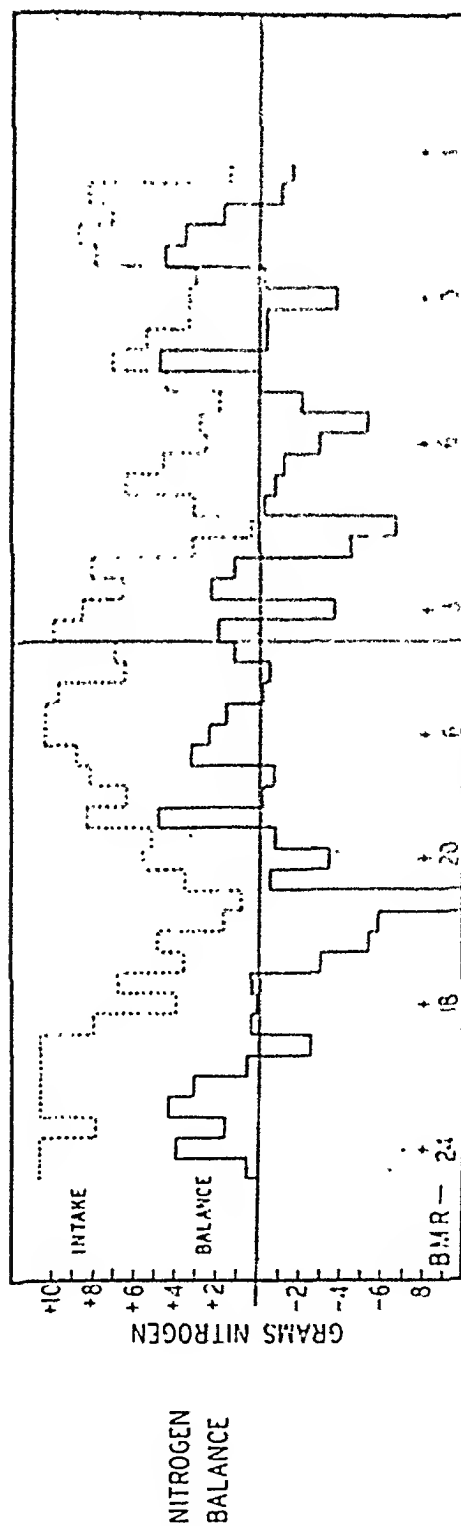


FIG. 1 (a)
 FIG. 1.—Blood counts, nitrogen balance and oxygen consumption in Case 1

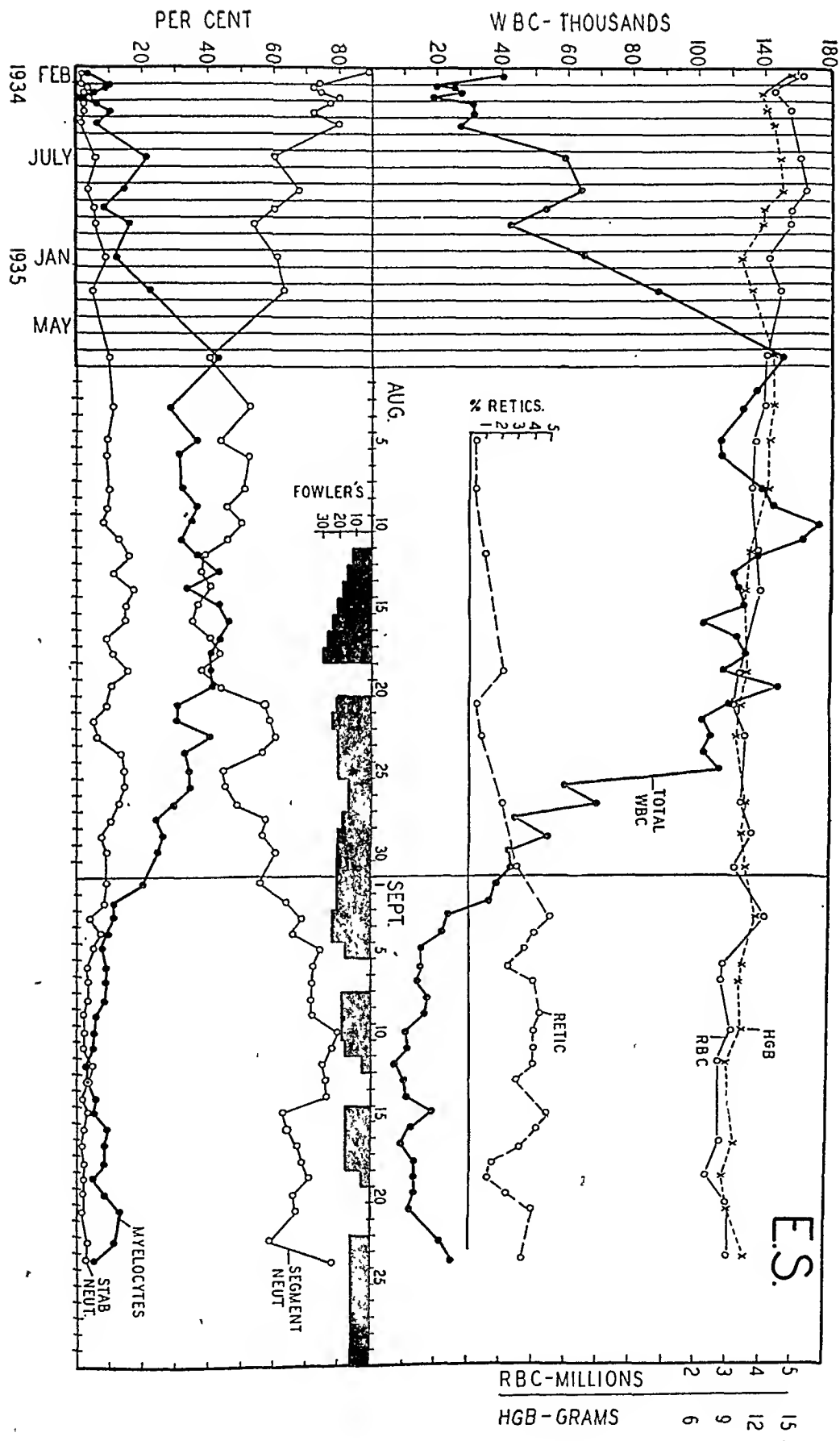


FIG. 1 (b).

In August, 1931, she reentered the hospital with acute arthritis of the left knee and subsequent involvement of other joints, thought to be gonorrheal in nature. Blood hemoglobin was 10.5 gm.; red blood cells, 4,300,000; white blood cells, 15,600 (eosinophils, 2%; basophils, 0.5%; neutrophils, 82.5%; lymphocytes, 12.5%; myelocytes, 2.5%). The acute joint symptoms gradually subsided, but arthritic deformities were added to those of the residual poliomyelitis.

In December, 1933, she presented herself with symptoms and signs of secondary syphilis. Dark-field examination of material obtained from ulcerative lesions in the mouth revealed *treponema pallida*. The Wassermann reaction, which had previously been negative, was 4+. Blood counts were as follows: hemoglobin, 12 gm.; red blood cells, 5,100,000; white blood cells, 13,000, of which 80% were neutrophils. No abnormal cells were found.

The administration of neosarphenamine was followed by an urticarial reaction. During the following 2 months intramuscular injections of bismuth were given. After receiving a total of 0.8 gm. of "Bismosol," she developed soreness of the mouth and throat, fever, chills and malaise, and again entered the hospital in February, 1934. The significant physical findings at this time, in addition to the skeletal deformities previously noted, included bilateral cervical lymphadenitis and swelling, redness and shallow ulcerative lesions of the tongue, buccal mucous membrane and palate. A marked metallic line was visible at the gum margins. The spleen was not palpable. Material from the ulcers showed many fusiform bacilli and spirilla. The blood Wassermann reaction was negative. A diagnosis of bismuth stomatitis with superimposed fusospirochetal infection was made. During convalescence from this illness immature granular cells were observed in the peripheral blood for the first time and the presence of early leukemia was suspected. During February and March, 1934, repeated hematologic observations were made. Blood hemoglobin was 14.5 gm.; red blood cells, 5,010,000. White blood cells varied between 19,000 and 40,000 (from 3 to 12% myelocytes, identified repeatedly in both fixed and supravitral preparations). For example, on March 5, 1934, the total leukocyte count was 35,600 (basophils, 4.5%; eosinophils, 0.5%; myelocytes, 11%; metamyelocytes, 2%; stab. neutrophils, 3%; segment neutrophils, 71%; lymphocytes, 7.5%; monocytes, 0.5%). Platelets were present in normal numbers. No abnormal red blood cells were found. Supravital (neutral red) differential count was as follows: basophils, 4%; eosinophils, 2%; "C" myelocytes, 11.5%; neutrophils, 75.5%; lymphocytes, 6%; monocytes, 1%. These and subsequent hematologic observations are summarized in Fig. 1. Biopsy of sternal bone marrow was done on March 8, 1934.

During the following 18 months, clinical and hematologic observations were made at intervals. The patient remained clinically well. There was gradual increase in the total white blood cell count and in the percentage of immature cells. On July 30, 1935, the total leukocyte count was 151,000 per c.mm. (basophils, 1%; eosinophils, 3.5%; myelocytes, 30%; metamyelocytes, 13%; stab. neutrophils, 41%; lymphocytes, 1.5%). She was without symptoms of any kind. The spleen, however, was felt for the first time, with the edge palpable 5 cm. below the costal margin. There was no lymph gland enlargement. The liver was not palpable. The blood Wassermann reaction was negative, although she had had no antiluetic treatment since January, 1934. On August 2, 1935, the patient was admitted to the hospital for detailed study of the effect of the administration of potassium arsenite.

After a preliminary 10-day period of control observation, Fowler's solution was given in rapidly increasing amounts and continued in sub-

toxic doses. Throughout the period of observation, she continued to feel well, except for recurring symptoms of mild arsenic intoxication. The latter consisted of anorexia, nausea and sometimes vomiting, itching of the eyes, periorbital edema and on one occasion a small area of dermatitis. These symptoms promptly cleared on decreasing or omitting the dose of Fowler's solution for a few days. During her hospital stay, the stools consistently showed occult blood. This was believed to be due to intermittent bleeding of the gums, a symptom which had been present since the bismuth gingivitis in January, 1934. Gastro-intestinal Roentgen-ray studies were negative. Bone marrow biopsy was done on August 8, 1935, before the administration of Fowler's solution was begun, and again on September 12, 1935, at the height of the hematologic remission.

CASE 2.—J. N., a 40-year-old laborer, had the diagnosis of chronic myelogenous leukemia made in 1932. The course of this patient's illness up to August, 1935, has been summarized elsewhere.³ Treatment between 1932 and January, 1936, had consisted of repeated courses of potassium arsenite and small amounts of Roentgen therapy, of which he had had a total of 2300 Roentgen units.

In January, 1936, he was readmitted to the Strong Memorial Hospital for detailed observation before and after Roentgen therapy. He had had no treatment for the past 3 months, during which time the white blood cell count had been rising. He had been without recent symptoms until 10 days before admission, during which time there had been increasing weakness and fatigue and an uncomfortable feeling of fullness in the left upper quadrant of the abdomen.

The temperature, pulse and respirations were normal. Significant physical findings included moderate pallor, small retinal hemorrhages, hepatomegaly and marked splenomegaly. There was no glandular enlargement.

Red blood cells numbered 3,960,000 per c.mm.; hemoglobin, 10.8 gm. per 100 cc.; white blood cells, 255,000 per c.mm. (basophils, 3%; eosinophils, 1%; myelocytes, 43%; metamyelocytes, 13%; stab neutrophils, 11%; segment neutrophils, 28%; lymphocytes, 1%). Two nucleated red blood cells were found in counting 100 leukocytes. The platelets were abundant. The urine showed a trace of albumin, with rare white blood cells. The blood Wassermann reaction was negative.

After a suitable control period, a total of 1000 Roentgen units were given over the chest and abdomen in divided doses during a period of 7 days. The blood counts, nitrogen balance and determinations of the basal metabolic rate are summarized in Fig. 2. Sternal bone marrow was obtained at biopsy on January 8, 1936, before Roentgen therapy and on February 13, 1936, at the height of the hematologic remission.

Comment. The first patient, E. S., was of particular interest because of the opportunity which was offered to follow the blood picture during the preclinical stage of the disease. It may be noted that the peripheral blood picture led to a suspicion of early myelogenous leukemia, confirmed by bone marrow biopsy, 18 months before the appearance of splenomegaly, which was the first clinical evidence of leukemia. The observations in this patient indicate that the bone marrow changes may precede the leukemic manifestations in the peripheral blood and emphasize the value of bone-marrow biopsy in the early diagnosis of the disease.

The results of treatment are summarized in Figs. 1 and 2. The only clinical changes noted in patient E. S., who was without

symptoms referable to leukemia, was decrease in the size of the spleen during the administration of solution of potassium arsenite. Roentgen therapy was followed by complete, but temporary, disappearance of symptoms in the case of J. N., and by decrease in the size of the spleen.

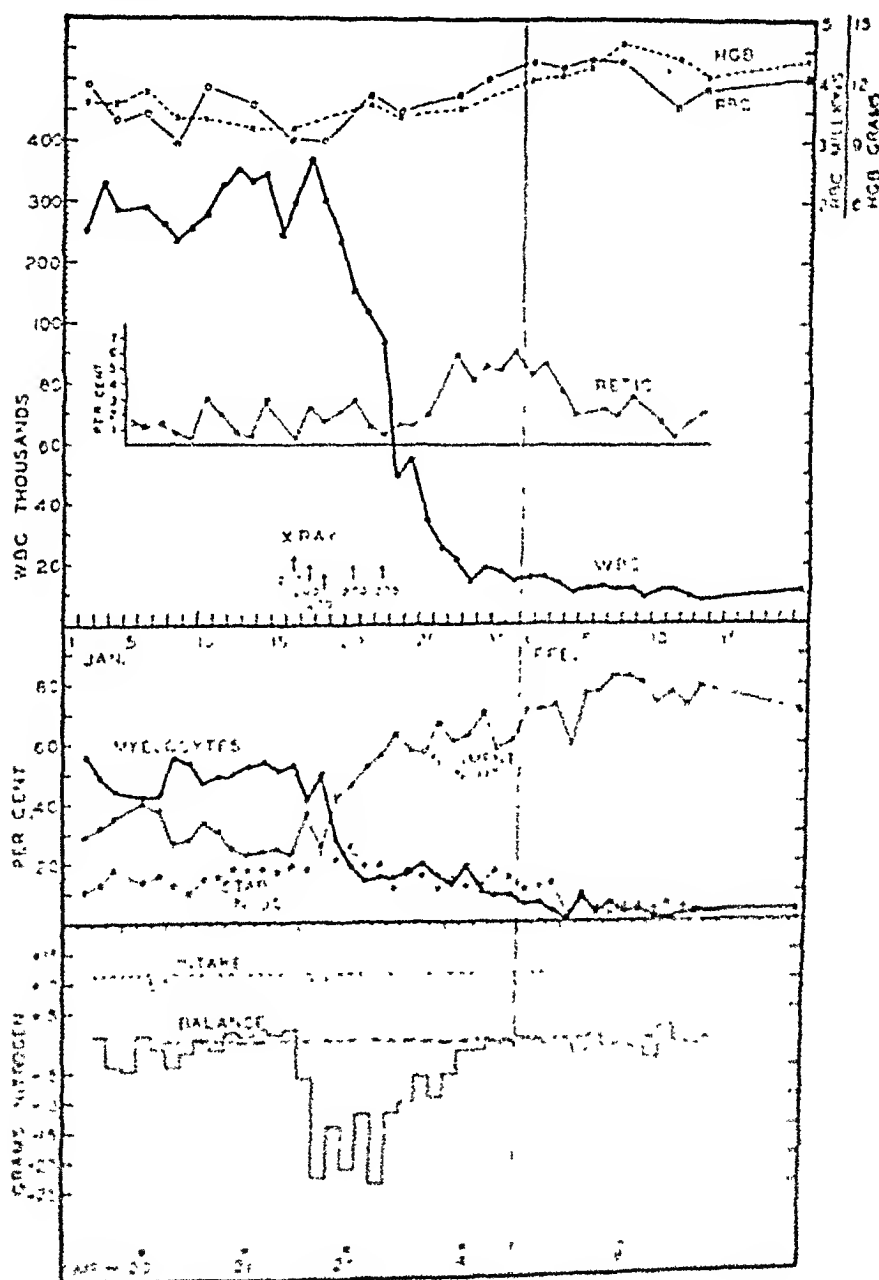


FIG. 2. Effect of Roentgen therapy on the course of the disease in the case of J. N.

The changes in the blood picture were similar in the 2 cases. The administration of both Roentgen therapy and of solution of potassium arsenite was followed by a precipitous decrease in the total leukocyte count to a normal level, a marked increase in the percentage of adult granulocytes and almost complete disappearance of immature cells from the peripheral blood. In each instance, improvement in the white blood-cell picture was followed by a significant increase in reticulocytes and by a subsequent rise in the hemoglobin and the red blood-cell count. No significant change occurred in the platelets.

TABLE 1.—PERIPHERAL BLOOD AND BONE MARROW DIFFERENTIAL COUNTS BEFORE AND AFTER TREATMENT.

	E. S.						J. N.			
	3-8-34.		8-8-35.		9-12-35.		1-8-36.		2-13-36.	
	Blood.	Mar-row.	Blood.	Mar-row.	Blood.	Mar-row.	Blood.	Mar-row.	Blood.	Mar-row.
Hemoglobin, gm. per 100 cc.	13.2	..	12.3	..	8.7	..	10.2	..	12.3	..
R. B. C., millions per c.mm.	4.64	..	3.84	..	2.74	..	2.93	..	3.87	..
W. B. C., thousands per c.mm.	26.9	..	139.0	..	7.4	..	237.0	..	8.5	..
Reticulocytes, %	0.4	..	4.0	..	0.8	..	2.0	..
Basophils	(%) 2.0	(%) ..	(%) 2.5	(%) 1.1	(%) 2.5	(%) 0.6	(%) 3.0	(%) 0.3	(%) 3.5	(%) 4.3
Eos. myelocytes	..	1.0	..	1.4	..	0.8	..	1.8	..	0.1
Eosinophils	1.5	1.6	2.0	2.8	2.5	6.1	1.0	3.6	0.5	2.1
Blasts	..	0.6	..	2.8	..	1.6	..	0.3	..	3.2
Myelocytes	9.0	28.4	23.5	33.5	2.0	7.7	46.5	28.2	2.0	14.6
Metamyelocytes	0.5	15.8	8.5	16.2	1.0	4.1	9.0	18.5	0.5	5.0
Metaneutrophils	3.0	20.0	10.0	15.1	4.5	11.7	13.0	24.8	2.5	10.4
Segment neutrophils	74.0	9.6	51.0	14.2	75.5	22.3	27.0	10.2	79.5	15.6
Megaloblasts	..	0.2	1.1	..	0.6	..	0.1
Erythroblasts	..	5.2	..	3.1	..	23.2	..	2.4	..	21.5
Normoblasts	..	3.6	..	2.8	..	8.1	..	1.8	..	6.1
Megakaryocytes	0.1	0.7	..	0.2
Lymphoid cells	10.0	13.2	2.5	3.6	11.5	6.2	0.5	2.0	11.5	11.5
Degenerated cells	..	0.8	..	3.3	..	6.5	..	4.3	..	5.3
Myeloid-erythroid ratio	8.6:1		14.7:1		1.7:1		18.2:1		1.9:1	

The first bone-marrow biopsy in the case of patient E. S. showed changes characteristic of chronic myelogenous leukemia. In the gross, the marrow was gray and appeared very cellular. The bony trabeculae of the normal sternal marrow had been almost entirely replaced by cellular tissue. The histologic sections showed closely packed masses of immature and adult granulocytes, with scattered erythropoietic elements and only an occasional fat space (Fig. 3). The differential count of the bone-marrow cells (Table 1) showed a marked increase in the myelopoietic elements, with a myeloid-erythroid ratio of 8.6 to 1. The second bone-marrow biopsy, taken 18 months later, but before the institution of therapy, showed more advanced changes, with fat spaces entirely absent and increase in

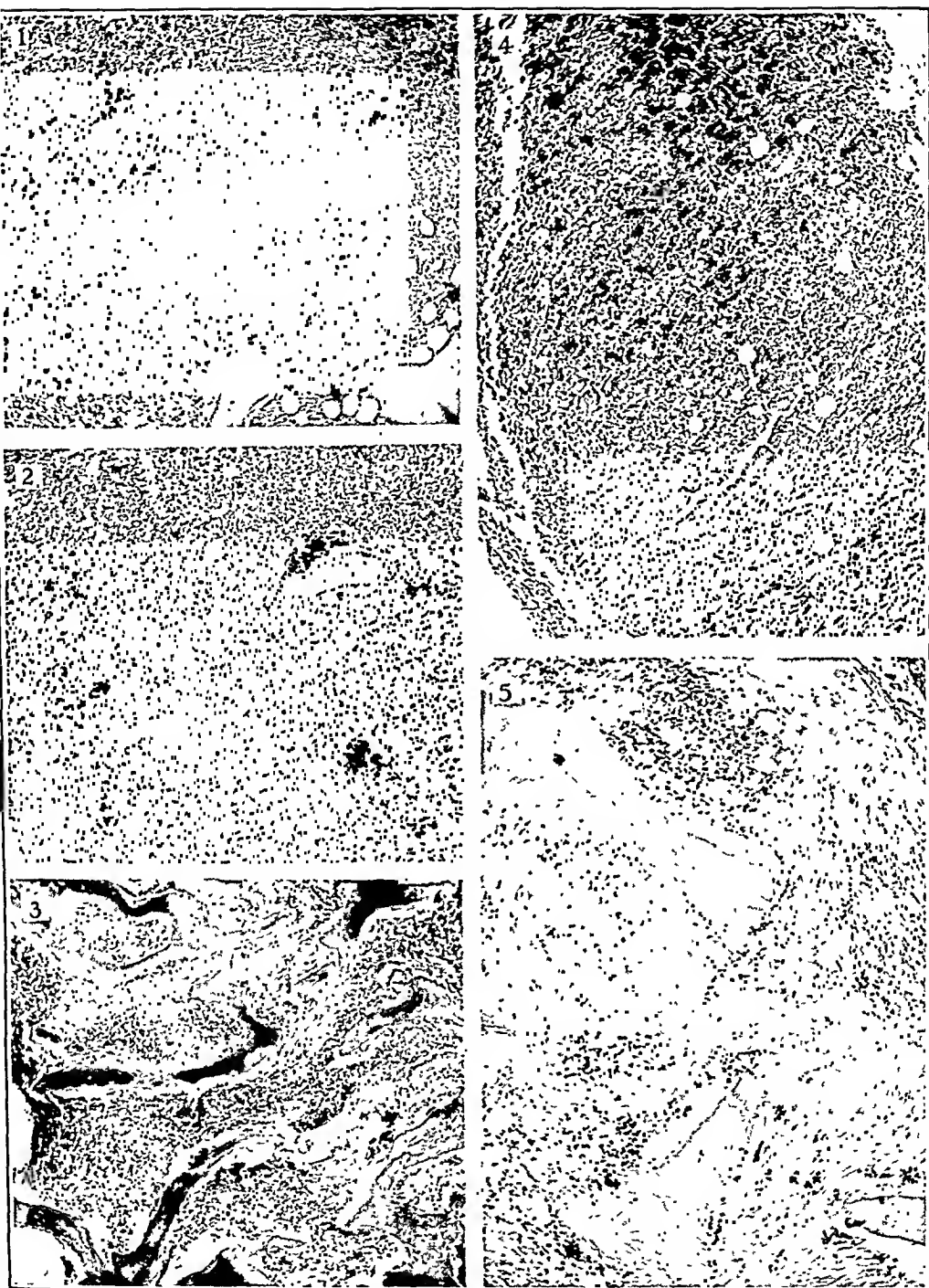


FIG. 3.—Photomicrographs of sternal bone marrow before and after treatment.
 (1) E. S., 3-8-34 ($\times 100$); (2) E. S., 8-8-35 ($\times 100$); (3) E. S., 9-12-35 ($\times 100$);
 (4) J. N., 1-8-36 ($\times 150$); (5) J. N., 2-13-36 ($\times 150$).

sidered, particularly in view of the connective-tissue reaction in the marrow cavity, is that the changes observed in the last biopsy in each instance, may have been due to tissue reaction resulting from the mechanical interference of the previous biopsy. This is considered unlikely, inasmuch as the later biopsies were made a distance of at least 3 cm. from the previous operative site. The changes observed in the bone marrow of these 2 patients, particularly as regards the differential counts, were compatible with the coincident changes in the peripheral blood, and were interpreted as being due to the therapeutic influence of the solution of potassium arsenite and the Roentgen therapy, respectively. Observations made in a larger number of cases will be necessary before it may be concluded that such changes are characteristic of therapeutically induced remissions in myelogenous leukemia.

The basal metabolic rate determinations showed changes similar to those reported elsewhere² and require little comment. Before treatment both patients exhibited a moderate increase in oxygen consumption, which fell to a normal level during remission.

The nitrogen balances are of interest because they constitute the only essential respect in which the response to the two therapeutic agents differed. Patient E. S., who received solution of potassium arsenite, showed no significant change in the nitrogen balance, although a marked decrease in the white blood-cell count was observed. On several occasions the nitrogen output exceeded the nitrogen intake. However, the periods of negative nitrogen balance, which was never of great magnitude, were of short duration and occurred at a time when the nitrogen intake was curtailed because of gastro-intestinal reaction to the large doses of Fowler's solution. Furthermore, during the period of rapid fall in the white blood-cell count, the excretion of nitrogen was slightly less than the intake. During the entire period of observation the nitrogen excretion exceeded the nitrogen intake by only 14.1 gm., a figure considered to be within the range of technical error. The weight decreased from 43 to 40.2 kg., the non-protein nitrogen of the blood was reduced from 38 mg. % at the beginning of the experiment to 26 at the conclusion of the period of observation. It may be concluded that, in this particular instance, the induction of a remission by the use of solution of potassium arsenite resulted in no significant change in the nitrogen balance.

It is well known that the use of Roentgen therapy in leukemia ordinarily is followed by an increase in the nitrogen excretion. This is usually interpreted as the result of the destruction of large numbers of white blood cells. Patient J. N. exhibited a marked negative balance during and after Roentgen therapy. During the period of observation, nitrogen excretion exceeded the nitrogen intake by 171.5 gm., the weight decreased from 74 to 70 kg., the non-

protein nitrogen of the blood dropped from 45 to 29 mg.%. Although the negative nitrogen balance persisted during the fall in the white blood cell count, it should be noted that the peak of nitrogen excretion occurred 2 days before there was any significant change in the leukocyte count. These observations, together with the fact that the irradiation of normal animals and of patients with malignant disease results in increased nitrogen elimination,⁴ suggests that the negative nitrogen balance observed after Roentgen therapy in leukemia is related primarily to effects other than those on the circulating leukocytes. Further observations will be necessary before definite conclusions may be ventured in this regard.

No attempt has been made to draw sweeping or generalized conclusions as to the effect of solution of potassium arsenite or Roentgen therapy on the bone marrow and nitrogen metabolism in this disease. Rather, the data are reported as detailed observations in two typical instances of chronic myelogenous leukemia, with characteristic remissions following treatment with these two agents. It is recognized that there are wide variations in both the clinical and hematologic picture of the disease and in the response to both forms of therapy. The question as to whether the observations made in these patients, particularly in regard to the changes in the bone marrow, represent the typical response in therapeutically induced remissions of the disease, must be decided by further investigation.

THE EFFECT OF THE SUBCUTANEOUS INJECTION OF ADRENALIN ON THE LEUKOCYTE COUNT OF SPLENECTOMIZED PATIENTS AND OF PATIENTS WITH CERTAIN DISEASES OF THE HEMATOPOIETIC AND LYMPHATIC SYSTEMS.*

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It is a well-known fact that the subcutaneous injection of adrenalin produces a leukocytosis in the peripheral blood. The mechanism of this action is still not definitely understood.

Oliver and Schäfer²⁶ found that an extract prepared from the suprarenal glands was capable of producing contraction of the spleen when injected into laboratory animals. Schäfer and Moore³⁰ showed that this extract produced a similar effect on the excised spleen of laboratory animals. Loeper and Crouzon²⁰ noted that, in both rabbits and man, the injection of adrenalin produced a slight but variable *decrease* in the red blood cell count, as well as an increase in the white blood cell count. They found also that the increase in the number of lymphocytes occurred earlier, and disappeared sooner, than that of the neutrophils.

Frey and his co-workers¹³⁻¹⁵ and also Hatiegan¹⁷ showed that in normal individuals a leukocytic response of distinctive character followed the injection of adrenalin. This response occurred in 2 phases: the first phase was noted soon after injection, and consisted of a sharp increase in the absolute and relative numbers of lymphocytes; the second followed at the end of an hour and consisted of a decrease in the number of lymphocytes and an increase in the neutrophils. Frey was unable to demonstrate this characteristic reaction in patients who had undergone splenectomy, or in those in whom the architecture of the spleen had been grossly altered by disease, such as, for example, in advanced Banti's syndrome. From these experiments he concluded: 1, that adrenalin induced leukocytosis by causing contraction of the spleen and the expression of blood cells into the general circulation; 2, that, since the lymphocytic response does not occur following removal of the spleen or when disease has caused widespread alteration in the structure of the organ, the test is of value in determining splenic function.

* Assisted by a grant from the Christine Breon Fund.

Barcroft²⁻⁴ showed that the spleen contracts following a number of altered physiologic conditions, including hemorrhage, asphyxia, exercise, and changes caused by psychic disturbances. From his observations he concluded that the spleen acts as a reservoir for blood cells which controls, to a certain extent, the volume of the circulating blood.

Investigations made since the studies of Frey have been the basis for diverse opinions. There is general agreement that injection of adrenalin produces leukocytosis, and that an increase in lymphocytes precedes that of neutrophils.

Attempts to explain the mechanism of leukocytosis following the injection of adrenalin have prompted the following hypotheses:

1. *Splenic Contraction.* Since the early work of Frey, it has been assumed that splenic contraction plays an important part in the production of the leukocytosis.^{1, 12-15, 18, 19, 21, 22, 24, 25, 26, 27, 28, 30} Numerous experiments and observations, however, have shown that contraction of the spleen is not necessary for the production of the leukocytosis, and that the leukocytosis may occur after the spleen has been removed.^{7, 9, 18, 22, 27-29, 31, 32}

2. *Hemoconcentration.* According to this hypothesis, the volume of the circulating formed elements of the blood can be increased relatively by a loss of plasma fluids into the tissues.³³ It has been demonstrated that adrenalin obstructs the venous outflow from the liver, increases the portal pressure, and favors the passage of fluid into the lymphatics of the liver, resulting in a concentration of the cellular elements of the circulating blood.^{1, 12, 13, 20} Yang and Chang²⁵ could find no significant changes in the volume of the blood following the use of adrenalin.

3. *Direct Stimulation of the Bone Marrow.* Walterhöfer³⁴ demonstrated changes in the bone marrow of rabbits following repeated injections of adrenalin. Auricchio³ and Edmunds and Stone¹⁷ considered the leukocytosis as *probably* due to direct stimulation of the bone marrow.

The leukoeytosis has also been attributed to stimulation of the vegetative nervous system;⁶ and likewise to the synergistic effect of alterations in the hydrogen-ion concentration within the hematopoietic organs and locally in the smaller blood vessels.^{9,21}

In an attempt to determine whether the leukoeytosis is due to direct stimulation of the hematopoietic organs or to an indirect action upon the peripheral vascular system, the effects of adrenalin stimulation on the leukocyte counts of 33 patients were studied. Seven patients who had undergone splenectomy were studied, for observation of the effect of removal of the spleen upon the results of the test. Four of these were tested before, as well as following, splenectomy. In addition, there were studied 7 patients diagnosed as having Hodgkin's disease; 7 with anemia and splenomegaly; 4 with luetic hepatosplenomegaly; 4 with tuberculous adenitis; and 4 with myeloid leukemia.

Methods. Each patient was injected with a single dose of 1 cc. of a 1 to 1000 solution of adrenalin hydrochloride (Parke-Davis), administered subcutaneously in the deltoid region. Blood pressure readings were taken shortly before, and 10 minutes after, injection. Most of the patients experienced the usual and characteristic reactions of anxiety, palpitation, hyperidrosis, tremor and elevated blood pressure. Some patients complained of soreness in the region of the spleen, and tenderness over the long bones.

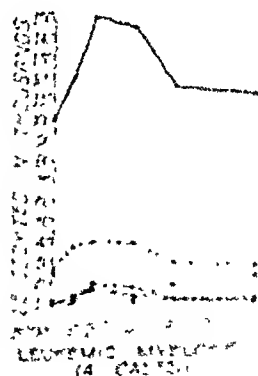
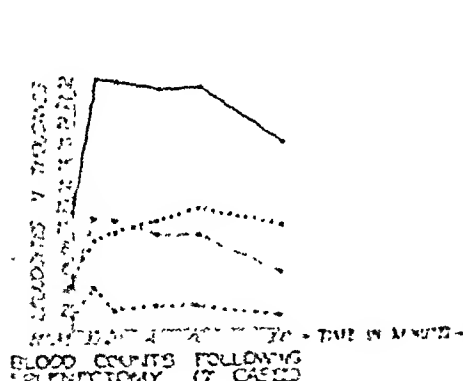
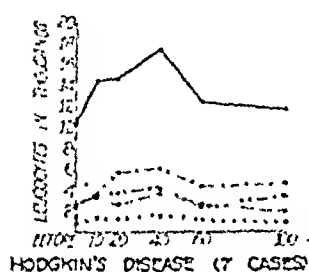
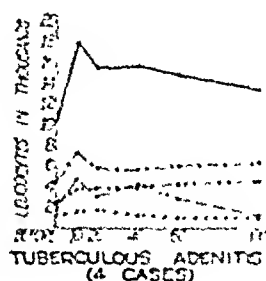
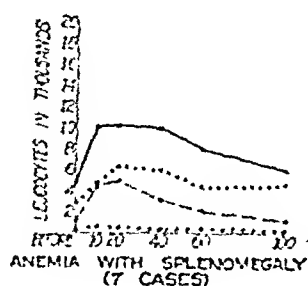
All blood counts were made using certified (U. S. Bureau of Standards) pipettes and hemocytometers. Differential blood counts were made on cover-slip preparations stained by the Jenner-Giemsa method. Complete studies of the capillary blood, including hemoglobin determination, erythrocyte, leukocyte, differential and platelet counts, were made before inoculation. Leukocyte and differential counts were made at intervals of 10, 20, 40, 60 and 100 minutes after inoculation.

In as many instances as possible the diagnoses were verified by pathologic examination of tissue removed by biopsy, and in 1 case by autopsy.

RESULTS. The results are shown graphically in the accompanying figure (Chart I). The values are expressed as averages in terms of absolute numbers of each cell type per cc. of blood. A description of the results in the patients studied following splenectomy, and those of the various diagnostic groups in our series, are given below:

1. *Following Splenectomy.* In the 7 patients who were tested following removal of the spleen, there was a slight leukocytosis (average 11,400) before the injection of adrenalin. Following the injection there was a rapid increase in number of leukocytes, so that at 10 minutes the total count was slightly more than doubled. The marked leukocytosis persisted to the end of an hour. At 100 minutes the total count had dropped, but was still considerably higher (average 18,000) than before the injection. The early rapid increase in the number of leukocytes was characterized by a marked lymphocytosis, an unusual feature of these cases. The neutrophils and monocytes also showed a considerable increase. At the end of 40 minutes the

lymphocytes and monocytes had decreased, but the neutrophils were still rising, reaching a maximum at the 60-minute count. The



Adrenalin tests were performed on 4 of these patients before, as well as following, splenectomy. In the tests performed before operation, the curve in no instance resembled that following splenectomy. It would appear, from these studies, that the subcutaneous injection of adrenalin in the splenectomized person produces a marked, persistent leukocytosis of normal blood cells characterized by a conspicuous lymphocytosis followed by a neutrophilia which persisted throughout the test.

In the following table are recorded the results of an adrenalin test done on a young boy of Greek parentage who had had his spleen removed 2 years previously and on whom the diagnosis of erythroblastic anemia had been established.

ADRENALIN TEST.

August 6, 1935.

S. P., male, aged 12. Parentage, Greek.

Diagnosis: Erythroblastic anemia; spleen removed, 1933.

Injection: 1 cc. 1/1000 adrenalin hydrochloride, subcutaneously.

	Before.	10 min.	20 min.	40 min.	60 min.	100 min. after.
Hemoglobin	40% (5.6gm.)					
Red blood cells (millions)	3.12					
Platelets	500,000	Great- ly incr.				
Nucleated red blood cells	77,100	84,100	98,700	105,700	90,600	74,000
White blood cells corrected	18,100	79,500	67,700	46,300	50,600	32,000
Neutrophils: Filamented	6,154	11,925	18,956	12,038	14,168	11,200
Non-filamented	543	795	677	320
Eosinophils	1,086	3,975	2,708	2,315	1,012	320
Basophils	362	506	320
Large lymphocytes	1,012	320
Small lymphocytes	7,602	47,700	38,589	22,687	25,806	14,080
Monocytes	1,991	12,720	3,385	6,482	6,578	4,800
Metamyelocytes	463		
Myelocytes	181	795	463	1,012	640
Blasts	2,031	926		
Unclassified	181	1,590	1,354	926	506	

In this case the leukocyte response is similar in type to that found in the group discussed above. The nucleated red blood corpuscle count reaches its highest level at 40 minutes and returns to the pre-injection level at 100 minutes. The maximum neutrophil count appears at 20 minutes, and the lymphocytes and monocytes reach their maximum in 10 minutes. At 100 minutes the levels of the latter three types of cells remain elevated in direct proportion to the degree of leukocytosis. When the immature types of leukocytes are studied as a group, one notes that at 20 and 40 minutes they are apparently increased out of proportion to the total leukocyte count.

2. *Anemia With Splenomegaly* (7 Cases). This diagnostic term is used in preference to the controversial one of "Banti's syndrome," although 4 of the 7 patients exhibited the disease-course which is usually regarded as typical of Banti's syndrome. Before injection a leukopenia was found in all patients. Following injection, there was a sharp rise in the total leukocyte count, so that at the end of 10 minutes the number of white blood cells had doubled. Within 60 minutes the total leukocyte count had fallen, and at the end of 100 minutes it showed a gradual trend toward the original level. The lymphocytes showed an early sharp rise followed by an early fall, so that within 100 minutes they had returned to the original level. The neutrophils increased more slowly, but the rise was sustained longer, and a slight secondary rise was noted between 60 and 100 minutes. The other cellular elements were not markedly affected.

3. *Tuberculous Adenitis* (4 Cases). Before administration of adrenalin, there was a slight elevation of the leukocyte count. Following the injection, there was a sharp increase in the total average count (from 10,500 to 18,000 in 10 minutes). By the end of 20 minutes there was a slight decrease and then a fairly well-sustained high level to 100 minutes. The increase in number of lymphocytes and of neutrophils occurred simultaneously with a relatively greater increase in the lymphocytes. Within 100 minutes, the lymphocytes had decreased in number to a point below the original level while the neutrophils showed a secondary increase between 40 and 100 minutes, and at 100 minutes had reached a level of 50% greater than before the injection. Contrary to the reports of other authors,^{22,25} we did not find a significant increase of monocytes. One patient with tuberculous cervical lymphadenitis complained of soreness and pain in the region of the affected lymph nodes after the injection of adrenalin.

4. *Hodgkin's Disease* (7 Cases). Before injection, there was a slight leukocytosis, with both absolute and relative neutrophilia. Within 10 minutes after the injection, there was a sharp increase in the total average leukocyte count (from 10,400 to 14,500). The highest count (average 17,500) was observed at 40 minutes. The neutrophils showed the greatest relative increase with a secondary rise, particularly of the non-filamented forms, between 60 and 100 minutes. The lymphocytes showed a secondary rise between 20 and 40 minutes, followed by a gradual return toward the normal level. In general, the curve of the monocytes paralleled that of the lymphocytes. In 1 case, a few primitive monocytes were seen. Three patients complained of pain in the region of the spleen, one of whom complained also of pain over the long bones. Autopsy of the patient last mentioned showed the bone marrow infiltrated with cells characteristic of Hodgkin's disease.

5. *Luetic Hepatosplenomegaly* (4 Cases). Before injection, the leukocyte counts were within normal limits. Within 10 minutes after the injection, a definite leukocytosis had occurred, the highest total counts being recorded at 20 minutes. The increase in number of lymphocytes was relatively greater than that of the neutrophils; however, the neutrophilia was sustained longer. The lymphocytosis at the 20-minute count was a conspicuous feature of these cases. After the first sharp increase, the lymphocytes showed a gradual decrease toward their original number. At 60 minutes, the neutrophil count had returned to the level found before injection. A secondary rise in the neutrophils was observed at 100 minutes. No immature cells were seen.

6. *Leukemic Myelosis* (4 Cases). The average total leukocyte count before the injection of adrenalin was 100,000. Following the injection there was a rapid rise to 150,000 white blood cells at 20 minutes. At 60 minutes the count was 112,000. The non-filamented neutrophils rose from an average of 27,000 before the injection to 40,000, 20 minutes after, and then showed a gradual return to the original level. The number of filamented neutrophils decreased slightly during the first 10-minute interval, then rose sharply at the 20-minute interval and gradually returned to the original level. The myelocytes increased from 9000 to 16,000 at 20 minutes and returned to 9000 at 100 minutes. The metamyelocytes followed a similar course. The myeloblasts were decreased in number following the injection, and then rose gradually to reach their original level within 100 minutes. From these studies one cannot say that the abnormal forms were specifically stimulated by the injection of adrenalin. All patients complained of pain in the region of the spleen. One patient complained of aching pain over the long bones, as well as pain over the ribs and sternum.

Discussion. While it was not our intention in this study to explain the mechanism of the leukocytic response to adrenalin, we believe that our results help to throw some light on this phenomenon. Most noteworthy is the fact that the blood of patients whose spleens had been removed exhibited a response which, in its general features, was not very different from that found by other investigators. This would indicate that, while the spleen may contract and discharge a relatively large volume of blood into the circulation, it cannot be the only causative factor in the phenomenon of leukocytosis following the injection of adrenalin.

Worthy of consideration also is the finding of very few immature cells in the peripheral blood. If it were true that the increase in white blood cells is due to the sudden expression of cells from the bone marrow into the general circulation, one would expect to find, especially in the myeloid leukemias, a fairly large proportion of immature cell forms. That such was not the case, is an argument against the hypothesis that stimulation of the bone marrow plays

an important rôle in the leukocytosis. A more probable explanation is that the increase in number of leukocytes is chiefly due to the redistribution of formed elements of the blood, or altered relationships between the volume of blood cells and plasma.

In each disease group studied, a somewhat different response was obtained. However, certain features were consistently noted. In all instances, there was a definite increase in the number of leukocytes following the subcutaneous injection of adrenalin. With few exceptions, the leukocytosis consisted entirely of an increase in the number of normal lymphocytic and granular cell elements. In general, except in the cases of myeloid leukemia, the lymphocytes showed an earlier and more rapid, as well as relatively greater, increase. The granular cells showed a later but longer-sustained increase, with a tendency toward a secondary rise.

Summary. 1. In all patients studied, the injection of adrenalin was followed by a definite leukocytosis.

a, The blood of patients who had undergone splenectomy showed a leukocytic response differing little from that of patients whose spleens had not been removed.

b, The lymphocytes showed an earlier and relatively greater increase than that of the other cellular elements.

c, With the exception of a case of erythroblastic anemia, immature cell forms did not appear in the circulation in numbers sufficient to warrant the conclusion that the bone marrow was stimulated.

2. The results of the adrenalin test in a patient who was diagnosed as having erythroblastic anemia and whose spleen had been removed is recorded.

3. As a result of these studies, no definite diagnostic value can be attributed to the leukocytosis which follows the subcutaneous injection of adrenalin.

REFERENCES.

- (1.) Auricchio, L.: *La Pediatria*, 31, 922, 1923. (2.) Barcroft, J.: *Lancet*, 1, 319, 1925. (3.) Barcroft, J., and Poole, L. T.: *J. Physiol.*, 64, 23, 1927. (4.) Barcroft, J., and Stephens, J. G.: *Ibid.*, p. 1. (5.) Benhamou, E., Jude, and Marchionni, R.: *Compt. rend. Soc. d. biol.*, 100, 458, 1929. (6.) Bertelli, G., Falta, W., and Schweeger, O.: *Ztschr. f. klin. Med.*, 71, 23, 1910. (7.) Beumer, H., and Hellwig, H.: *Monatschr. f. Kinderh.*, 22, 457, 1921. (8.) Binet, L., Cardot, H., and Fournier, B.: *Compt. rend. Soc. d. biol.*, 96, 521, 1927. (9.) Bostrom, E. F.: *Am. J. Physiol.*, 58, 195, 1921. (10.) Clark, G. A.: *J. Physiol.*, 66, 274, 1928. (11.) Dazzi, A.: *Morgagni Arch.*, 63, 93, 1921. (12.) Edmunds, C. W., and Stone, R. P.: *Arch. internat. de pharm. et therap.*, 28, 391, 1924. (13.) Frey, W.: *Ztschr. f. d. ges. exp. Med.*, 3, 416, 1914. (14.) Frey, W., and Hagemann, E.: *Ztschr. f. klin. Med.*, 92, 450, 1921. (15.) Frey, W., and Lury, S.: *Ztschr. f. d. ges. exp. Med.*, 2, 50, 1914. (16.) Griffith, F. R., and Emery, F. E.: *Proc. Soc. Exp. Biol. and Med.*, 26, 628, 1929. (17.) Hatiegan, J.: *Wien. klin. Wchnschr.*, 30, 1541, 1917. (18.) Kagi, A.: *Folia Haemat.*, 25, 107, 1920. (19.) Lamson, P. D.: *J. Pharm. and Exp. Therap.*, 16, 125, 1920. (20.) Loeper, M., and Crouzon, O.: *Arch. d. méd. exp.*, 16, 83, 1904. (21.) Loeper, M., Decourt and Lesure: *Compt. rend. Soc. d. biol.*, 94, 272, 1926. (22.) Martin, H. E.: *J. Physiol.*, 75, 113, 1932. (23.) McLaughlin, A. R.: *J. Pharm. and Exp. Therap.*, 34, 147, 1928. (24.) Menkin, V.: *Am. J. Physiol.*, 85, 489, 1928. (25.) Miller, D. K., and Rhoads, C. P.: *J. Clin. Invest.*, 12, 1009, 1933. (26.) Oliver, G., and Schäfer, E. A.: *J. Physiol.*, 18, 230, 1895. (27.) Patek, A. J., and Daland, G. A.,

AM. J. MED. SCI., 190, 14, 1935. (28.) Radosavljevic, A., and Sekulic, M.: Wien. Arch. f. inn. Med., 20, 81, 1930. (29.) Sanguinetti, A.: Policlinico (sez. med.), 28, 97, 1921. (30.) Schäfer, E. A., and Moore, B.: J. Physiol., 20, 1, 1896. (31.) Schenk, P.: Med. Klin., 16, 279, 309, 1920. (32.) Simonin, P., Florentin, P., Hennequin, L., and Entcheva, V.: Compt. rend. Soc. de biol., 110, 1158, 1932. (33.) Stein, P.: Ztschr. f. klin. Med., 108, 567, 1928. (34.) Tournade, A., and Chabrol, M.: (a) Compt. rend. Soc. d. biol., 90, 835, 1924; (b) Ibid., 96, 390, 1927. (35.) Walterhofer, G.: Deutsch. Arch. f. klin. Med., 135, 208, 1921. (36.) Weil, P. E., and Isch-Wall, P.: Presse méd., 37, 1357, 1929. (37.) Yang, C. S.: Chinese J. Physiol., 2, 163, 1928. (38.) Yang, C. S., and Chang, H. C.: Ibid., 4, 21, 1930.

OTHER REFERENCES CONSULTED.

Barcroft, J.: Features in the Architecture of Physiological Function, Cambridge, The University Press, 1934. Benhamou, E.: L'exploration fonctionnelle de la rate, Paris, Masson et Cie, 1933. Dalla Palma, B.: Minerva Medica, 2, 397, 1930. Dalla Volta, A.: Arch. di Patol. e Clin. Med., 15, 34, 1935. Izquierdo, J. J., and Cannon, W. B.: Am. J. Physiol., 84, 545, 1928. Krumbhaar, E. B.: AM. J. MED. SCI., 182, 764, 1931. Sabrazes, J., and Saric, R.: Angines lymphomonocytaires, agranuloctoses, leucemies leucopeniques, Paris, Masson et Cie, 1935. Scimone, V.: Minerva Medica, 9, 777, 1929. Weil, P. E., and Gregoire, R.: Compt. rend. Soc. d. biol., 100, 637, 1929.

PAROXYSMAL COMPLETE HEART BLOCK ALTERNATING WITH NORMAL RHYTHM AND CONDUCTION.

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COMPLETE auriculoventricular heart block alternating with normal rhythm and conduction is regarded as an unusually rare occurrence. Its rarity can be judged by the fact that complete heart block itself is an uncommon disorder, only being found in approximately 0.55% of cases with known or suspected cardiovascular disease.^{6,12} It is the purpose of this study to review critically the reported cases of this type of paroxysmal complete heart block and to present a new one. The present case first showed periods of complete heart block with Adams-Stokes' syndrome which alternated with periods of normal conduction and later developed a chronic complete block with the coincident disappearance of the syncopal attacks.

Review of Literature. Criteria. It is obvious that graphic records are necessary to establish proof that paroxysmal *A-V* block exists (White).³⁰ Consequently only those reports which had either polygraphic or electrocardiographic records were studied, and in these the graphic tracings were examined in detail. Only those cases were selected in which there was clear evidence that normal conduction and complete heart block with an idioventricular rhythm existed independently and periodically. The occurrence at times of an additional partial block, a frequent finding in these

cases, was not an eliminating factor. A *P-R* interval of 0.20 second or less was regarded as normal. Cases in which the block was in the nature of a ventricular standstill without a subsequent idioventricular rhythm were not included. It was felt that such cases did not belong in a group in which an independent ventricular rhythm was definitely established.

Summary of Cases. Twenty cases previously included or potentially falling into this group were found in the literature. Of these, only 12 met with the established criteria. The remaining 8 have been excluded for reasons to be given herewith. Gibson and Ritchie,¹¹ and Gager⁷ each reported a potential case. The former was excluded because of insufficient graphic evidence, the latter because the *P-R* interval during normal rhythm was slightly prolonged (0.24 second). Gossage's¹³ case was eliminated because there was no clear evidence that complete *A-V* dissociation existed. The cases of Starling²⁷ and Lewis^{17a} showed ventricular standstill with no definite idioventricular rhythm. No graphic evidence was presented in Case 1 of Mackintosh and Falconer¹⁹ to establish the transient nature of the complete heart block which developed the day after admission and persisted. In Case 2 of the same authors, however, there was sufficient evidence to warrant its inclusion in this series. The case report by Cohn, Holmes, and Lewis⁵ contained two tracings, both of which showed only a high degree of partial block. In a case reported by Wilson and Robinson³¹ normal conduction was not established until long after the complete heart block had disappeared.

The more important data of the acceptable 12 cases and of the present case have been tabulated for convenience in Table 1. This table needs no further explanation other than to mention that some of the data have been estimated from the published tracings when such data were not specifically mentioned in the text.

Pathology. The heart was examined after death in only 4 cases of this series. In the case of Gager and Pardee⁸ a calcified ring was found around the left auriculoventricular orifice. The bundle of His was grossly normal but there was no histologic examination and consequently little of definite value is contributed by this report. Russell-Wells and Wiltshire³⁴ found a heart with calcified aortic cusps and a fibrocalcereous mass in the left upper ventricular septum. Histologically, the *A-V* node and the bundle of His were in immediate contact with this mass. The tissue of the node and bundle showed the effects of chronic inflammation and, in addition, there was an area showing the presence of subacute inflammation. The coronary vessels were not particularly sclerotic. These authors concluded that the encroachment of the mass plus fluctuating degrees of inflammation on the basis of an infectious endocarditis, type not determined, had been responsible for the clinical findings. In the case reported by Yater and Willis,³⁴

FIG.
1

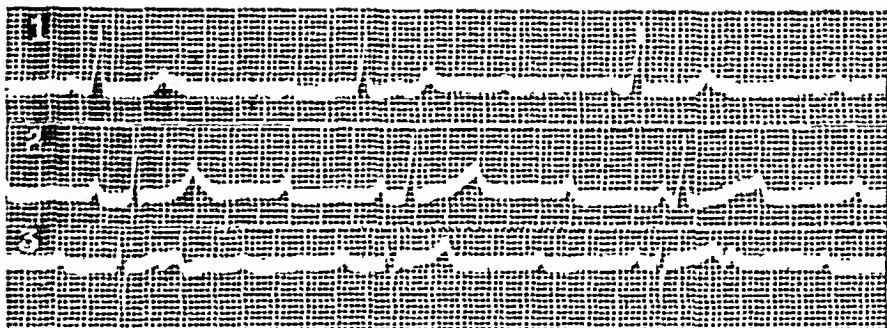


FIG.
2

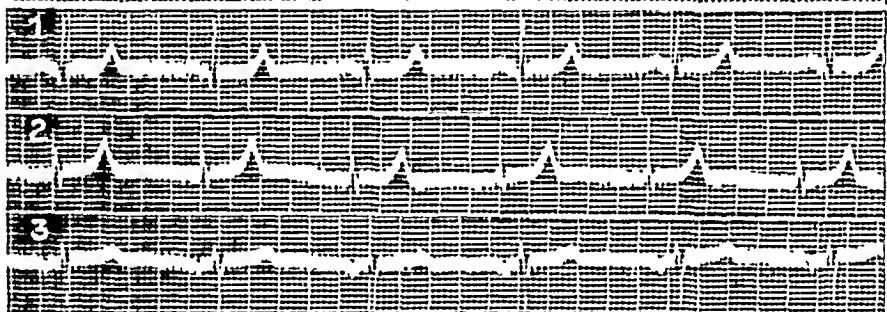


FIG.
3

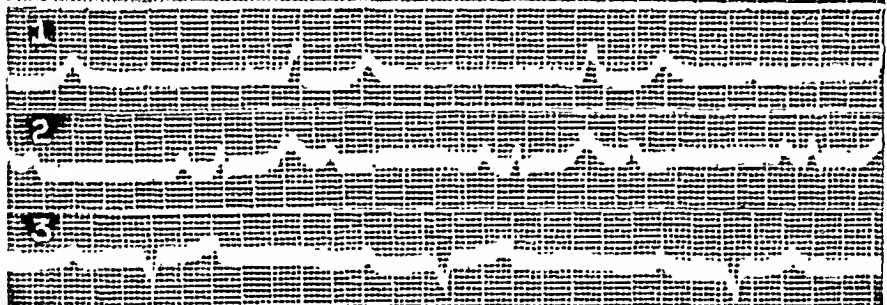


FIG. 1.—Transient complete heart block.

FIG. 2.—Normal rhythm. *P-R* interval 0.18 second

FIG. 3.—Chronic complete heart block.

TABLE 1.—CASES OF PAROXYSMAL COMPLETE HEART BLOCK.

Cases.	Age at onset.	Sex.	Duration.	Etiology.	Graphic tracings.										Notes.	Outcome with time after onset.
					Ecg or poly-gram.	Normal.		Complete heart block.			Additional partial block.	Other findings.				
						Rate per min.	P-R or A-C	QRS.	Rate per min.	QRS.						
													A	V		
1. Thayer and Peabody; Earnshaw (Case 1)	53 yrs.	M	5 mos.	? Arteriosclerosis	P	70 to 80	.18 to .20	..	120 to 130	30	..	High degree	Nor. conduction foll. by vent. standstill. Then an idiovent. rhythm. Then part. block. Right bundle-branch block in comp. block (Fig. 2)*	Atrop. grs. 1/60 abolished part. block. Atrop. grs. 1/30 had no effect on comp. block. Atrop. grs. 1/100 t.i.d. gave relief from A-S attacks	Well.	
2. Mackintosh and Falconer ¹⁹ (Case 2)	71	M	3 yrs.	Arteriosclerosis	P	..	.20	..	81	20	.192	High degree	Nor. conduction foll. by vent. standstill. Then an idiovent. rhythm. Then part. block. Right bundle-branch block in comp. block (Fig. 2)*	Atrop. grs. 1/100 t.i.d. gave relief from A-S attacks	Died in convulsions (3½ yrs.).	
3. Simon and Robinson ²³	65 yrs.	M	3½ yrs.	Arteriosclerosis*	ECG	56 to 84	.19 to .20	.145 to .159	73*	49 to 51	Normal*	Aur. fibrillation in comp. block (final state) Partial rt. bundle-branch block with both nor. rhythm and comp. block	Atrop. grs. 1/50, exercise, and vagal pressure had on effect on comp. block on	Died (3½ yrs.).	
4. Russell-Wells and Wiltshire ²¹	41 yrs.	M	12 yrs.	Infectious endocarditis	ECG	62 to 82	.20	Normal*	75*	16 to 30	.15	High degree	Comp. block vent. tachycardia; then standstill and shift of pacemaker from rt. vent. to A-V node	Atrop. 2 mgm. had no effect on block. Vagal pressure decr. rate from 67 to 52 and incr. P-R from .18 to .20.	Died of en. of cocum (12 yrs.). Died . Last 1 mos. no attacks (3½ yrs.).	
5. Carter and Dinnidge ²	67 yrs.	M	3½ yrs.	Arteriosclerosis*	ECG	78	.17	.12	78	30	.15	High degree	Comp. block vent. tachycardia; then standstill and shift of pacemaker from rt. vent. to A-V node	Atrop. grs. 1/100 l.i.d. abolished attacks for 1 wk. (? specific effect*). Epineph. abolished attacks caused vent. tachycardia	Died in convulsions (7 mos.).	
6. Gager and Pardee ⁸	59 yrs.	M	7 mos.	Rheumatic heart disease*	ECG	60 to 72	.18 to .19	.10*	85 to 100	18 to 40	.12	High degree	Aberrant vent. complexes with varying forms. Vent. and cardiac standstill in comp. block 2-to-1 heart block shifting to comp. block	Atrop. grs. 1/100 l.i.d. abolished attacks for 1 wk. (? specific effect*). Epineph. abolished attacks caused vent. tachycardia	Died in convulsions (3 mos.).	
7. Yater and Williams ²⁰	74 yrs.	M	3 mos.	Arteriosclerosis	ECG	80*	.19*	.08*	120	54*	.08	High degree	Aberrant vent. complexes with varying forms. Vent. and cardiac standstill in comp. block 2-to-1 heart block shifting to comp. block	Epineph., oculocardiac and vagus reflexes, no effect. Atrop. and amyl nitrite produced part. block. Barium chloride temporarily effective	Died of heart failure (14 yrs.).	
8. Wolferth and McMillan ²²	18 yrs.	F	11 yrs.	ECG	80 to 110*	.16 to .21	.10*	100*	30 to 40*	.08 to .10	High degree	Aberrant vent. complexes. Left bundle-branch block in nor. rhythm (constant). Rt. bundle-branch block in comp. block on one occasion	Atrop. .25 mgm. s. c. thyroid and oxygen, no effect. Epineph. 0.5 cc. i. v. caused vent. tachycardia.	Well for 3 mos. (nor. conduction).	
9. Carter and McEachern ³	60 yrs.	M	2½ yrs.	Arteriosclerosis	ECG	53 to 78	.18 to .21	.11	58 to 65	21 to 33	.13 to .16	Aberrant vent. complexes with varying forms. Irreg. vent. rhythm	Atrop. .25 mgm. daily abolished attacks (? specific effect*)	Well	
10. Cheer and T'Ang ⁴	66 yrs.	M	5 mos.	Acute arthritis ? rheumatic ? infectious	ECG	83 to 107	.18 to .19	.08	120	18	.08	Aberrant vent. complexes with varying forms. Irreg. vent. rhythm	Atrop. .25 mgm. daily abolished attacks (? specific effect*)	Well	
11. Weiss and Ferris ²² (Case 1)	51 yrs.	M	10 yrs.	Esophageal diverticulum	ECG	48 to 66	.17 to .21	.08*	39*	18*	.08*	Slight degree at times	Aberrant vent. complexes with varying forms. Irreg. vent. rhythm	See summary under Pathology	Well with atrop. (gr. 1/120 t.i.d.).	
12. Sachs and Traynor ²³	43 yrs.	M	3 mos.	Rheumatic heart disease (?)	ECG	68 to 88	.16 to .18	.08*	120 to 110*	17 to 19	.10 to .12*	Aberrant vent. complexes with varying forms. Irreg. vent. rhythm	Atrop. grs. 1/30, thyroid, barium chloride and vagal pressure had no effect	Well on discharge (normal conduction).	
13. Present on 10 yrs.	78 yrs.	F	2 mos.	Arteriosclerosis ? old coronary thrombosis	ECG	60 to 80	.18 to .20	.06 to .08	97 to 68	29 to 35	.06 to .10	Absent Q-wave Lead 1 in comp. block	Ephedrt. grs. ¼ 4 i.d. abolished seizures*. Atrop. grs. 1/60 t.i.d. no effect	Well in chronic complete block.	

* Personal interpretation. New terminology is used in bundle-branch block.

a bar of calcium was found extending across the interventricular septum compressing the bundle of His. It was found histologically that a large portion of the bundle was invaded by fibrous tissue. At no point, however, was the conduction system entirely interrupted for an intact group of fibers was followed in every serial section. There was moderate atheromatosis of the coronary arteries with constriction of some of the smaller branches. Wolferth and McMillan,³² on gross examination of their heart, found a small area of fibrosis in the septum near the branching of the bundle of His. Histologically, there was interstitial fibrosis with a very slight amount of early calcification involving the main branch below the *A-V* node and both bundle branches. The lesion, however, failed to destroy the bundle completely, for the posterior one-eighth remained intact and appeared normal. There was evidence of coronary sclerosis but grossly the lumina of the vessels were not narrowed.

The pathologic findings in Starling's²⁷ case are mentioned here because reference to these will be made later. In this case Lewis^{17b} found, in addition to thickened calcified aortic cusps, a fibro-calcareous mass fixed to what had probably been the right anterior aortic cusp. This mass formed a saddle over which the bundle of His divided. Histologically, this mass had damaged the lower segment of the main bundle as well as the right and left branches. There was complete destruction of the conducting tissue in this area with replacement by fibrous tissue. The coronary arteries were found to be dilated and markedly sclerotic.

In the case reported by Weiss and Ferris,²⁹ an esophageal diverticulum was clearly shown to be the causative factor. With distention of the diverticulum by means of a rubber balloon there occurred ventricular standstill accompanied by an Adams-Stokes' attack which was followed by an irregular idioventricular rhythm. With deflation of the balloon the rhythm returned to normal. Epinephrine and ephedrine abolished the seizures but the complete heart block developed as before. There was no ventricular standstill, however, and the idioventricular rhythm became regular. Atropine abolished both the Adams-Stokes' attacks and the complete heart block; the latter being replaced by a partial block as manifested by a moderately prolonged *P-R* interval. From these and other studies the authors concluded that a sensory branch in the adjacent vagus trunk was stimulated by the distention of the diverticulum and a vagovagal reflex ensued which caused a complete *A-V* dissociation.

Case Report. On June 17, 1935, a 76-year-old widowed Lithuanian housewife was admitted to the Boston City Hospital. She had been in good health for many years until 4 weeks before admission. At that time she began to have short sudden attacks of dizziness, heaviness in the head, momentary loss of consciousness with mild twitchings of the extremities followed by fleeting blindness. These attacks were not related to exertion, swallowing, or changes in position. There was no cause to which she could attribute them. The attacks became more frequent until she was having

5 to 7 daily. There were no other central nervous system or cardiorespiratory symptoms.

Aside from the cardiovascular system, the only positive physical findings (including the neurologic examination) were a divergent strabismus of the right eye with bilateral weakness of the internal rectus muscles (old), a palpable liver edge, and a moderate dorsal scoliosis.

Cardiovascular System. The heart was not enlarged or displaced. The rate was 42 per minute and the rhythm regular. The heart sounds were very distant. In diastole there could be heard from one to two muffled sounds and these gave the definite impression of coming at regular intervals. It was also noted that the mitral first sound was occasionally louder than in the preceding beat. A soft systolic murmur was heard over the entire precordium, loudest at the apex. There was slight sclerosis and tortuosity of the peripheral vessels. The ophthalmoscopic examination revealed slight vascular changes in the retinal arteries. The blood pressure was 115/40 mm. of Hg.

Laboratory. The red blood cell count was 3,600,000 per c.mm. with a hemoglobin of 68% (S). The white blood cells were normal in number and type. Except for a few white blood cells, repeated urines were negative. The blood N.P.N. was normal. The blood Kahn and Hinton reactions were negative. A lumbar puncture revealed normal pressure and dynamics; there were no cells; the spinal fluid protein was 34 mg.% and the colloidal gold curve 0123210000. The spinal fluid Kahn reaction was negative.

Roentgen Ray Examination. Heart measurements: R.M. 4 cm.; L.M. 8.8 cm.; I.D.C. 30.1 cm.; G.V.B. 4.8 cm. Interpretation: aorta tortuous and sclerotic. Old healed tuberculosis left upper chest. Spine shows marked dorsal scoliosis.

Diagnosis. The patient was, at first, considered to be a case of chronic complete heart block with Adams-Stokes' attacks. The day following admission it was noted that the heart rate had risen to an unusually high level for an idioventricular rhythm. In addition, it was found that during this high rate the muffled diastolic sounds were absent and the heart sounds were loud and distinct in contrast to those found on admission. A paroxysmal heart block was suspected and two electrocardiograms taken on the day following admission revealed the unusual condition present.

Electrocardiographic Tracings. The published electrocardiograms are in general typical of several taken during each phase of the patient's course. Later electrocardiograms taken during chronic complete heart block, however, did show the disappearance of the tendency toward left bundle branch block and the low amplitude of the Q-R-S complexes which are present in Figure 3. In addition, a tracing taken in Lead 4 showed an absent Q wave which strongly suggests an old coronary occlusion.

The Effect of Atropine and Ephedrine. During a 4-day control period the patient recorded her seizures. There were from 3 to 7 Adams-Stokes' attacks daily with an average of 5 per day. Atropine (grs. 1/60) was then given 3 times daily for 3 days with no effect. Five days later ephedrine (grs. $\frac{3}{4}$) was given 4 times daily and continued for 3 days (no toxic symptoms) with only 1 attack early on the day that this therapy was started. The dose of ephedrine was then diminished to grs. $\frac{3}{8}$ three times a day, but since the patient began having attacks again the ephedrine was increased after 4 days to the former dosage. This was continued for 10 days during which time the patient had no attacks. At the end of this period it was discontinued for the purpose of special electrocardiographic studies with atropine and ephedrine.

At the time when these studies were made it was not realized that the complete A-V dissociation had become permanent. When atropine (grs. 1/60) was injected intravenously the auricular rate rose from 72.4 to

77 beats per minute and the ventricular rate rose from 37.5 to 38.7 beats per minute. An acceleration of the ventricular rate in complete heart block after the injection of atropine correlates with Gilchrist's¹² findings. After the injection of ephedrine (grs. $\frac{3}{4}$) intravenously there was no change in either the auricular or ventricular rates.

Outcome. Ephedrine was never resumed and when the patient was last seen in December, 1935, 5 months after the discontinuance of ephedrine, she had had no Adams-Stokes' attacks and her heart had continued to beat within a range of 28 to 35 beats per minute.

COMMENT. When the graphic tracings in this case are correlated with the clinical findings a definite sequence of events is suggested. The patient passed through a period of approximately 6 weeks during which time normal rhythm alternated with complete heart block. There was ventricular standstill with Adams-Stokes' attacks probably during the transition from normal conduction to complete block.

Since atropine did not abolish the Adams-Stokes' seizures during this period it can be concluded with a fair degree of certainty that the vagus played no significant rôle in the fundamental mechanism of this case. The results with ephedrine demonstrate that unusually large doses of this drug are at times necessary to irritate the ventricle sufficiently to enable it to assume an independent pacemaking function in time to prevent the occurrence of Adams-Stokes' attacks.

The basic lesion, apparently organic, was progressive and finally destroyed, at least functionally, an entire section of the bundle of His, thus establishing a chronic complete *A-V* dissociation with an ectopic ventricular pacemaker. With the establishment of a stable ventricular pacemaker, the transitional period between complete auricular and complete ventricular control disappeared. Thus, the immediate cause of the Adams-Stokes' syndrome was abolished and there resulted a spontaneous symptomatic cure.

Form of the Transition. To obtain graphic records in these cases of the transition from one degree of conduction to another is obviously difficult and, for the most part, a matter of chance unless the attacks are frequent or can be induced. None were obtained in the present case. However, in this series, there were 4 cases in which such tracings were obtained.

In Case 2 of Mackintosh and Falconer the change was abrupt from normal conduction to a ventricular standstill which was then followed by an irregular idioventricular rhythm. The transition back to normal was accompanied by a high degree of partial block. Weiss and Ferris found that the abruptness with which the pressure was raised or lowered in the esophageal diverticulum of their patient was the factor determining the presence of partial block in the transition. With a slow change in pressure a partial block developed; with a sudden change there was an abrupt transition from normal conduction to a ventricular arrest. In the case reported by Cheer and T'ang the 4 idioventricular beats were preceded by ventricular

standstill and followed by an abrupt transition to normal conduction with a rapid rate. A tracing published by Wolferth and McMillan showed a 2 to 1 block with a normal *P-R* interval shifting to complete *A-V* dissociation without an intermediate ventricular standstill and presumably without an Adams-Stokes' attack.

From these few graphic observations it would seem that the ventricular standstill and syncope occur after the sudden cessation of normal rhythm and persist until an idioventricular rhythm is established. The last observation, however, shows that the transition from normal to an idioventricular rhythm by means of an intermediate high-grade block may not be accompanied by ventricular standstill or an Adams-Stokes' attack. There is also the possibility of ventricular standstill with symptoms occurring during the course of the idioventricular rhythm. The return from complete heart block to normal conduction is variable but probably not accompanied by asystole or syncope.

Clinical Features. Several clinical facts in recurrent complete heart block which are important diagnostically and therapeutically should be emphasized. The possibility arises that paroxysmal complete heart block may not be an uncommon precursor of complete heart block. Consequently, a paroxysmal complete heart block should be suspected in all cases of Adams-Stokes' syndrome, particularly early in the disease. The finding of a relatively high pulse rate in a case of complete heart block is strong evidence that an intermittent block may exist. The periodic appearance and disappearance of diastolic muffled auricular systolic sounds which may be accompanied by marked differences in the intensity and distinctness of the heart sounds furnish valuable clinical clues for the diagnosis of this condition. Electrocardiograms must be taken to establish a definite diagnosis. Although certain drugs may abolish the Adams-Stokes' attacks in these cases, the possibility of the establishment of a permanent complete heart block with the spontaneous disappearance of the syncopal seizures should be kept in mind.

Pathogenesis. There are various factors capable of causing variations in auriculoventricular conduction. All of these are not clearly understood. That complete *A-V* dissociation with an idioventricular rhythm can be established through vagal stimulation alone has been clearly shown in the case studied by Weiss and Ferris. That vagal stimulation can also be a contributory factor in the presence of organic disease is strongly suggested in Starling's case by the association of ventricular standstill and Adams-Stokes' attacks with swallowing, and the abolition of the seizures with atropine. Lewis pointed out a significant fact in this case, *viz.*, that although results with atropine may give evidence that the vagus is responsible for the occurrence of transient complete block, it cannot be definitely concluded from this test that the vagus is the only factor involved. The vagus factor is again strongly suggested in Case 2 of Mackintosh

and Falconer since relief of symptoms was obtained with atropine. The marked alternating changes in *A-V* conduction which occasionally accompany the two phases of Cheynes-Stokes respiration are also best explained on a vagal basis. Pathologic involvement of the vagus nerve has in itself been given as a cause of heart block in several cases.^{14,20}

Gallemaerts⁹ reported a remarkable case in which a transient complete heart block was definitely associated with orthostatic changes. His patient developed a temporary complete block with Adams-Stokes' attacks when the position was changed from recumbent to sitting or standing. The only other abnormality of conduction in this case was the constant finding of a slightly prolonged *P-R* interval (0.24 second). Atropine had no effect. Lutembacher¹⁸ reported a similar case in which a partial heart block was associated with orthostatic changes. Alexander and Bauerlein¹ reported a case in which an irregular rhythm with a rate of 42 beats per minute and a *P-R* interval ranging from 0.24 to 0.40 second in the supine position is changed to a regular rhythm with a rate of 94 and a *P-R* interval of 0.24 second when the patient is within approximately 15 degrees of the vertical position. The attacks of dizziness and the high degree of partial heart block have been relieved by atropine. Such findings offer much in the way of interesting speculation as to the factors responsible for fluctuations in auriculoventricular conduction.

A recurrent transient degree of inflammation in the bundle of His may possibly best explain the fluctuations in auriculoventricular conduction in Cases 10 and 12. In view of the calcification found at the aortic orifice at postmortem, subacute inflammation, although present, is not necessary to explain the clinical picture in Case 4. From the clinical findings in these cases and the postmortem findings in Case 4 the etiology of any inflammatory changes is not clear. The assumption of a rheumatic etiology is possibly warranted because of indirect evidence that it may have existed in these cases and because of the known fact that this disease has a particular affinity for the conduction system. However, from the evidence at hand this assumption cannot be made with any degree of assurance and, as a result, it seems only safe to say that complete heart block alternating with normal rhythm *may* result from infection. Furthermore, whether or not recurrent transient degrees of inflammation can cause this condition without there being another factor damaging the bundle of His, as in Case 4, can only be determined by further pathologic evidence in such cases.

There is an additional and larger group among these cases in which another common etiologic mechanism may be postulated (Cases 1, 2, 3, 5, 7, 9 and 13). This group for the most part includes patients of advanced years who have direct or indirect evidence of arteriosclerosis.

Norris in his discussion of Earnshaw's²⁸ case suggested the basis for the ensuing explanation of the fluctuating function of auriculo-ventricular conduction in this group. These cases probably have an organic process partially destroying a portion of the *A-V* node or main bundle. That the organic lesion in this group is usually either a fibrocalcereous mass at the base of the aortic valve, or an area of fibrosis due, most likely, to a coronary infarction of greater or less degree, is made quite probable by the fact that such findings are not uncommon in the hearts of individuals of this age group. In addition, these lesions are among the most frequent pathologic findings in complete heart block and in the present group. The literature on complete heart block due to fibrocalcereous lesions has been recently summarized by Yater and Cornell.³³

The tone of the remaining undamaged conducting fibers determines the degree of auriculoventricular conduction. As long as the tone of these fibers is maintained by adequate nourishment they are able to transmit auricular impulses in a normal manner. However, as soon as changes in the local circulation occur which deprive these fibers of adequate metabolic exchanges, a partial or complete block develops. The extent of the block will depend upon the amount and duration of the nutritional impairment. Géraudel¹⁰ in recent years has offered pathologic evidence that certain cases of heart block may be on a circulatory basis. He reports 2 cases of complete heart block, one of which was intermittent, in which serial sections of the conducting system showed no lesion. In both of these cases, however, he demonstrated a definite arteriosclerotic narrowing of the artery leading to the bundle of His.

If the organic lesion is progressive a section of the main conducting system will eventually be destroyed and a permanent complete heart block will be established. In this connection, however, as well as in the chronic block which developed in the present case, it must be remembered that discrepancies exist between the function of auriculoventricular conduction and the extent of the histologic damage in the bundle of His. Apparently permanent and, certainly, long periods of complete heart block have been observed in cases which showed partial or no destruction of the conducting system.^{10,15,16,21-23}

Summary. 1. The literature of recurrent complete heart block alternating with normal conduction and accompanied by Adams-Stokes' syndrome has been examined critically. Of 20 potential cases discovered in the literature, 12 have been accepted as complying with the criteria established. The important clinical, pathologic, and electrocardiographic data of these cases have been summarized.

2. A case, a woman aged 78, with Adams-Stokes' syndrome, is presented in which, as shown by electrocardiographic evidence, complete heart block alternated with normal rhythm and conduc-

tion. The results with atropine demonstrated that the changes probably occurred independent of any vagus effect. This case ultimately developed a chronic complete block with the spontaneous disappearance of the syncopal attacks.

3. The form of the transition from one degree of conduction to another, as shown by graphic tracings, is summarized.

4. The practical diagnostic and therapeutic considerations of this condition are emphasized.

5. The pathogenesis of paroxysmal complete heart block is discussed. It is probable that the majority of cases are on an arteriosclerotic basis and that either a fibrocalcereous mass or fibrosis due to coronary sclerosis partially damages the bundle of His. The fluctuating character of the conduction in these cases is probably determined by temporary variations in the local circulation to the remaining intact fibers.

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Addendum.—While this report was in press an additional case has been observed. A 57-year-old male was admitted to the Massachusetts General Hospital, complaining of 3 to 10 fainting attacks daily for a period of 2 months. Until this illness he had been in good health for many years. There were no cardiovascular symptoms. Physical examination was negative except that at times a slow heart rate (35 to 45 beats per minute) accompanied by auricular sounds was present. The electrocardiograms showed complete heart block ($Q-S$ 0.07) alternating with normal rhythm ($P-R$ 0.17, $Q-S$ 0.07). Repeated trials of carotid sinus stimulation during normal rhythm caused slight sino-auricular slowing without alteration in the $P-R$ interval, but failed to produce auriculoventricular block. While on the ward his heart rate fluctuated between 35 and 100 beats per minute. These fluctuations in rate and his attacks became progressively less frequent. At the end of 2 weeks a heart rate of 35 to 40 per minute seemed permanently established and his attacks ceased. When seen a month after discharge his heart rate was 35 beats per minute and there had been no recurrence of the attacks.

In a recent report Gilchrist (*Brit. Med. J.*, 1, 203, 1937) states that he has observed 8 cases of this type. Only 2 of these are reported in detail.

REFERENCES.

- (1.) Alexander, H. L., and Bauerlein, T. C.: *Am. Heart J.*, 11, 223, 1936.
- (2.) Carter, E. P., and Dieuaide, F. R.: *Bull. Johns Hopkins Hosp.*, 34, 401, 1923.
- (3.) Carter, E. P., and McEachern, D.: *Ibid.*, 49, 337, 1931.
- (4.) Cheer, S. N., and T'Ang, T. K.: *China Med. J.*, 46, 1081, 1932.
- (5.) Cohn, A. E., Holmes, G. M., and Lewis, T.: *Heart*, 2, 241, 1911.
- (6.) Ellis, L. B.: *Am. J. Med. Sci.*, 183, 225, 1932.
- (7.) Gager, L. T.: *Virginia Med. Monthly*, 59, 300, 1932.
- (8.) Gager, L. T., and Pardee, H. E. B.: *Am. J. Med. Sci.*, 169, 656, 1925.
- (9.) Gallemaerts, V.: *Arch. d. mal. du coeur*, 16, 332, 1923.
- (10.) Géraudel, E.: *The Mechanism of the Heart and Its Anomalies*, London Baillière, Tindall, and Cox, pp. 233, 250, 1930.
- (11.) Gibson, G. A., and Ritchie, W. T.: *Edinburgh Med. J.*, 2, 315, 507, 1909 (abstr. *Lancet*, 1, 533, 1909).
- (12.) Gilchrist, A. R.: *Quart. J. Med.*, 2, 483, 1933.
- (13.) Gossage, A. M.: *Heart*, 1, 283, 1910.
- (14.) Holst, P. F., and Monrad-Krohn, G. H.: *Quart. J. Med.*, 4, 49S, 1911.
- (15.) Hume, W. E.: *Heart*, 5, 149, 1913-14.
- (16.) Krumbhaar, E. B.: *Arch. Int. Med.*, 5, 583, 1910.
- (17.) Lewis, T.: (a) *Mechanism of the Heart Beat*, 2d ed., New York, Paul B. Hoeber, p. 35S, 1920; (b) *Lectures on the Heart*, New York, Paul B. Hoeber, p. 104, 1915; (c) *Heart*, 9, 283, 1922.
- (18.) Lutembacher, R.: *Arch. d. mal. du coeur*, 12, 145, 1919.
- (19.) Mackintosh, A. W., and Falconer, A. W.: *Heart*, 2, 222, 1911.
- (20.) Mallard, J., Dumas, A., and Rebattu, J.: *Arch. d. mal. du coeur*, 4, 29S, 1911.
- (21.) Oppenheimer, B. S., and Williams, H. B.: *Proc. Soc.*

Exp. Biol. and Med., 10, 86, 1912-13. (22.) Pepper, W., and Austin, J. H.: AM. J. MED. SCI., 143, 716, 1912. (23.) Rénon, L., Géraudell, E., and Thibault, D.: Bull. de la Soc. méd. des hôp. de Paris, 35, 56, 1913. (24.) Russell-Wells, S., and Wiltshire, H. W.: Lancet, 1, 984, 1922. (25.) Sachs, A., and Traynor, R. L.: Am. Heart J., 9, 267, 1933. (26.) Simon, S., and Robinson, G. C.: J. Missouri Med. Assn., 14, 97, 1917. (27.) Starling, J. H.: Heart, 8, 31, 1921. (28.) Thayer, W. S., and Peabody, F. W.: Arch. Int. Med., 7, 289, 1911; Earnshaw, H. C.: AM. J. MED. SCI., 139, 503, 1910. (29.) Weiss, S., and Ferris, E. B.: Arch. Int. Med., 54, 931, 1934; Weiss, S., Ferris, E. B., and Capps, R. B.: Trans. Assn. Am. Phys., 49, 177, 1934. (30.) White, P. D.: Heart Disease, New York, The Macmillan Company, 1931. (31.) Wilson, F. N., and Robinson, G. C.: Arch. Int. Med., 21, 181, 1918. (32.) Wolferth, C. C., and McMillan, T. M.: Am. Heart J., 29, 4, 521, 1928. (33.) Yater, W. M., and Cornell, V. H.: Ann. Int. Med., 8, 777, 1935. (34.) Yater, W. M., and Willius, F. A.: Am. Heart J., 4, 280, 1928-29.

VAGAL REFLEX IRRITABILITY AND THE TREATMENT OF PAROXYSMAL AURICULAR TACHYCARDIA WITH IPECAC.

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PAROXYSMAL auricular tachycardia frequently occurs in subjects without demonstrable cardiac lesions and with a normal or fair degree of cardiac reserve. Even in such cases effective treatment is of practical importance, not only because the unexpected appearance of the attacks often results in demoralization of the patient, but also because the condition often interferes seriously with his occupation unless the attacks can be promptly checked.

A number of therapeutic measures are alleged to have beneficial effects in the treatment of paroxysmal auricular tachycardia. White¹⁰ states, however, that "the very fact that there are many different drugs and therapeutic measures recommended for the immediate treatment of paroxysmal tachycardia shows that there is not one really satisfactory treatment." The purpose of this communication is 1, to demonstrate that ipecac is a suitable agent for the relief of the attacks, and 2, to analyze the underlying principle in the treatment of paroxysmal auricular tachycardia.

Among the therapeutic measures advocated are rest, induced sleep, bending, turning of the head, stooping with the head low, pressure over the "vagus," the carotid sinus or the eyeballs, and induction of "Valsalva" or "Müller" experiments. Digitalis, strophanthin, quinine, quinidine, morphine, apomorphine, acetylcholine and acetyl- β -methylcholine are some of the drugs used. Any of these measures may be effective in one patient but not in another,

and a measure previously beneficial may have to be intensified in order to abolish subsequent attacks, or may even become ineffective.

That the vagus nerves play an important rôle in paroxysmal auricular tachycardia has been appreciated for some time. Practically all measures capable of abolishing paroxysmal auricular tachycardia possess also the characteristic of increasing the cardiac vagal tone. It is known that paroxysmal auricular tachycardia results from the sudden activation of an ectopic focus in the auricle, with or without circus movements. Such an ectopic auricular pacemaker, by its faster inherent rate, gains control of the cardiac cycle. In order to reestablish normal sino-auricular rhythm, one can therefore attempt to reduce the excitability of the auricular myocardium with drugs such as quinine or quinidine. These substances, however, are more effective in preventing the attacks than in abolishing them. The most effective way to eliminate the activity of the ectopic focus and to reestablish normal rhythm is through the induction of powerful vagal inhibition of the auricles. Hence, the problem of the treatment of paroxysmal auricular tachycardia is to a large extent identical with the problem of increasing the cardiac vagal tonus.

The Use of Ipecac. Some 10 years ago, in the search for a simple and effective vagal stimulant for the treatment of paroxysmal auricular tachycardia we selected ipecac, since it is known to contain several alkaloids with emetic effect, which act both peripherally and centrally.^{2b}

We have used ipecac in 11 cases,* ranging in age from 16 to 54. In 4 cases rheumatic and in 1 case hypertensive heart disease was the underlying cause of the attacks, and in 6 cases no organic heart disease could be detected. The diagnosis of paroxysmal auricular tachycardia was usually confirmed by means of electrocardiographic tracings. In addition to these patients personally treated, we know of a large group of patients treated successfully by other physicians.

Dosage. From 1 to 4 drams (4 to 16 cc.) of syrup of ipecac administered orally proved to be the minimal effective dose. If an initial dose of 1 to 2 drams produced no vomiting or the desired effect, the dose was repeated in 45 minutes. Fresh and potent preparations should be used in view of the fact that considerable variation exists in the potency of various specimens of the syrup tested. While we have not used other ipecac preparations, they may well be equally efficacious.

Results. In all our cases this medication proved to be effective. In 1 case, however, doses of 1 and 2 drams, which relieved several attacks while the patient was under our observation, were later claimed to be ineffective. The physician reporting this lack of response failed subsequently to administer larger amounts; hence one

* Since this paper was submitted for publication we have treated 3 additional patients successfully with ipecac. In 2 of these patients no organic heart disease was present and the attacks followed surgical manipulation of the uterus. In the third patient rheumatic heart disease with mitral stenosis was present.

cannot state whether or not the drug failed. We know of 2 additional cases treated by others in which it was claimed that the medication was ineffective. Our observations indicate that, just as with other drugs used in the treatment of paroxysmal auricular tachycardia, the dosage may have to be raised with progressive severity of the seizures in the same patient, and the effective dosage varies considerably for different patients.

Following the administration of the effective dose, nausea and vomiting usually developed within 10 to 45 minutes. Simultaneously, preceding or following the retching or vomiting, the heart rate slowed down rather abruptly, and finally changed to normal sinus rhythm. We have had opportunity to hear the rapid heart sounds and to feel the rapid pulse change rather abruptly to a rate of 40 to 60, associated with loud heart sounds, full pulse and some sinus irregularity ("vagal beats"). One to 2 minutes thereafter a somewhat more rapid and a regular sinus rhythm became established. The fact that vomiting was induced but the attack was not abolished does not necessarily indicate failure of the medication. We have observed instances in which mechanically induced vomiting or vomiting induced with 1 dram (4 cc.) of syrup of ipecac failed to abolish the tachycardia, while subsequent administration of 2 drams (8 cc.) or more stopped the attack. Our experience indicates that usually the dose should be raised until vomiting occurs, but the minimal emetic dose may still be inadequate for the reestablishment of sinus rhythm. In some cases, local irritation from the stomach precipitates vomiting and eliminates the medication before it can be absorbed. For reestablishment of sinus rhythm the more powerful combined peripheral and central vagal stimulation is often required, and this can be induced only with higher dosage. Such higher dosage is often followed by a sensation of nausea and other evidences of parasympathetic stimulation of from 1 to 4 hours' duration.

Once the dosage of ipecac is established, it can be used by the patient without hospitalization or medical supervision. This not only represents an economic advantage, but is helpful in alleviating the constant dread of attacks and of isolation from a physician. The fact that the nausea and vagal stimulation in general last for some time, depending on the dosage, makes the effect of the drug more secure. Measures which stimulate the vagus for a short time frequently slow down the heart only temporarily and they fail to abolish the attack regularly. With the exception of weakness accompanying the nausea, and mild diarrhea, no untoward effects have been observed in the patients treated personally. We know of a patient treated in another institution who was relieved of an attack of paroxysmal auricular tachycardia but subsequently developed peritonitis. Autopsy revealed a ruptured subdiaphragmatic abscess. In this very unusual case it was assumed that the vomiting was responsible for the rupture of the previously unrecognized

abscess. Since the drug is administered orally, its emetic effect is a safeguard against toxic overdosage.

We have made no study of the efficacy of ipecac as compared with other measures. In all our cases, however, some of the other methods, such as calisthenic motions, pressure on the carotid sinus and over the eyeballs, and mechanically induced vomiting, had failed. In addition, drugs such as digitalis, morphine and acetyl- β -methylcholine had also been used in some of the cases before ipecac was administered. Our experience with acetyl- β -methylcholine is similar to that of Starr.⁵ In several instances the dosage had to be raised to a level which was associated with alarming transient manifestations. We believe, however, that ipecac should be used only after the simpler physical measures have failed.

It should be recalled that drugs such as morphine, apomorphine, digitalis and acetyl- β -methylcholine, which frequently abolish paroxysmal auricular tachycardia, often produce nausea or vomiting. This emetic action depends in part upon vagal stimulation. Thus in all these measures the basic underlying mechanism may well be the same, namely, vagal stimulation.

Mackenzie^{3a} makes no mention of ipecac in the treatment of paroxysmal tachycardia. In reporting Case 68, however, a 27-year-old man suffering from "paroxysmal tachycardia probably due to auricular flutter," Mackenzie mentions that this patient had been using wine of ipecac for some years before he learned about it in 1910.^{3b} Mackenzie subsequently observed the efficacy of this treatment in the patient. It is almost certain that this case was an instance of paroxysmal auricular tachycardia rather than of auricular flutter. Schilder,⁴ in 1934, advocated the induction of vomiting in the treatment of paroxysmal auricular tachycardia. He has successfully used a 1% solution of copper sulphate, of which he administered a "spoonful" at 5-minute intervals until the onset of vomiting. He mentions that at times one observes beneficial results with ipecac. These are the two casual remarks on the use of ipecac in paroxysmal auricular tachycardia that we were able to find in the literature.

Case Reports. CASE 1.—A surgeon of 54 was seen in consultation in May, 1932, because of increasingly frequent attacks of paroxysmal tachycardia. He had had no important infections in youth except typhoid fever at the age of 15 and severe sore throats, for which his tonsils were removed when he was 40. At college it was discovered that he had a heart lesion which, when he was first seen by us in 1932, was found to be rheumatic aortic regurgitation with moderate cardiac enlargement. On Roentgen ray examination the aorta was found to be greatly dilated, probably as a result of the aortic regurgitation. In spite of the cardiac lesion he had always been very active, both professionally and as a sportsman, being up to the present time a cup-winning golfer. He had had his first attack of paroxysmal tachycardia 8½ years ago, and several of these attacks had occurred at intervals of several months or years. When seen the first time he was having an attack of rapid, regular heart action at a rate of 160, which had persisted for 24 hours; no previous attack had lasted for more than 8 hours. Electrocardiogram

showed paroxysmal tachycardia with left axis deviation and slight slurring of the Q-R-S complexes. The attack ended spontaneously a few hours later.

During the next 3 years various measures were tried to prevent the attacks—quinidine (from 3 to 9 grains a day), digitalis, sedatives, purine derivatives; reduction of coffee, tea, tobacco, alcohol and golf; removal of foci of infection; colonic irrigations; and the study of basal metabolism and possible allergic factors by skin tests. In October, 1934, he began to have anginal pain on exertion and this became so uncomfortable whenever attacks of paroxysmal tachycardia were present that it was necessary to give him morphine with each one. The attacks lasted on an average for 13 hours, and he was finally put to bed for several weeks to regain cardiac reserve. Following this, he was able to continue his work, with very restricted exertion. The attacks were frequently repeated, one lasting 70 hours when he was on a West Indian cruise. His plans were disrupted by these attacks and he was continually apprehensive lest one appear. Attacks frequently came on early in the morning, required morphine and the installation of a trained nurse in the home, and, at best, would keep him away from his practice for from 1 to 5 days. It became impossible to rely on quinidine because of the onset of tinnitus and a sensation of fullness in the head when only 3 grains a day were given.

On April 1, 1935, an attack started after breakfast and he was instructed to induce vomiting by putting his finger down his throat, a procedure which he could do with ease. Vomiting occurred but the tachycardia persisted. Stimulation of the carotid sinus was attempted with no effect as far as the tachycardia was concerned, but with the production of a rather disturbing attack of scotoma, hemianopsia, and slight numbness of the right arm lasting about 20 minutes. Three doses of mechoilin, 7, 7 and 15 mg., given subcutaneously at 15-minute intervals, caused flushing of the face, pressure in the chest, thumping of the heart and a drop in blood pressure from 135 mm. to 80 mm. systolic. It was thought unwise to continue with larger doses since the beneficial effect from mechoilin is usually secured coincidentally with the fall in blood pressure. Syrup of ipecac was then suggested. Two drams were given, 30 minutes later 4 drams, and 15 minutes thereafter 8 drams. After several waves of severe nausea active vomiting and retching occurred, and at this moment the attack stopped, the pulse rate returning to 80.

On May 2, 1935, an attack started which was terminated in 20 minutes by the patient himself, who immediately took 4 drams of ipecac. Retching continued for 45 minutes. On June 1 this was repeated, the attack being ended at 7 o'clock, 10 minutes following onset, by the use of 4 drams, and he was able to operate at 9 o'clock.

Since that time ipecac has been used successfully by this patient approximately 40 times. The demonstrable saving of heart beats in the first year was estimated as being in the neighborhood of a million. In the presence of organic heart disease the importance of this is obvious.

CASE 2.—A 22-year-old theatrical worker entered the hospital in February, 1927, having been admitted before on several occasions with paroxysmal auricular tachycardia, as indicated by the electrocardiograms. The physical examination revealed no abnormality of the cardiovascular system. Previous attacks were usually relieved by stooping. The present one lasted for 6 days and could not be relieved by physical measures. Quinidine, grains 3, every 3 hours for 6 doses, and intravenous strophanthin, grains 1/120, failed. Spontaneously induced vomiting also remained ineffective. Three drams of syrup of ipecac produced severe nausea and vomiting and 50 minutes later the attack ceased. The heart rate dropped from between 210 and 220 to 80. Two months later the patient returned with a similar attack. Administration of ipecac again promptly relieved the tachycardia.

CASE 3.—A 38-year-old housewife was observed in 1928 with an "attack of palpitation." She had had similar attacks on several occasions, lasting from several hours to several days, and associated with precordial distress, radiating to the left arm. Physical examination (including the arterial pressure) was normal. The patient was observed during several of these attacks. Electrocardiograms revealed paroxysmal auricular tachycardia with a rate of 200 or over. The $Q-R-S$ interval was 0.06 second and the T waves were upright in all leads. Induced vomiting and morphine (grains $\frac{1}{8}$) subcutaneously were ineffective. Full digitalization of the patient produced nausea and vomiting, and with the onset of these symptoms the attack stopped. The patient continued to vomit and remained nauseated for 24 hours. An electrocardiogram taken subsequently revealed sinus rhythm with a rate of 50. A subsequent attack of tachycardia was relieved one-half hour after the administration of 2 drams of ipecac. The change in rhythm occurred simultaneously with the onset of retching.

CASE 4.—A 16-year-old student was first admitted in 1930, and again on numerous occasions with attacks of rapid heart rate associated with mild precordial pain, dyspnea, and feeling of coldness in the hands and feet. These attacks came on day or night. There was a history of rheumatic fever. Physical examination revealed malar flush; the apex impulse was prominent with systolic thrill and murmur over apex; the maximal left border was 11 cm. in the fifth space. Roentgen ray examination revealed rheumatic deformity of the heart. The arterial pressure was 90/60. Electrocardiograms on several occasions indicated paroxysmal auricular tachycardia with a rate of 200 or over. Following the attacks there was a sinus rhythm with a rate of 70 to 80, $Q-R-S$ interval 0.12 second, $P-R$ 0.24, high P_1 and P_2 .

The patient was observed in several attacks. The earlier ones were relieved by straining, bending or other bodily calisthenics, but later ones failed to respond to these measures, or to carotid sinus pressure or induced vomiting. One or 2 drams of syrup of ipecac regularly relieved these attacks within 15 to 30 minutes.

In 1935, the patient was observed by a physician who reported that 1 dram of ipecac, which had previously been effective, now failed to control the attacks. No larger dose of ipecac was administered; instead, the efficacy of acetyl- β -methylcholine was tested. On one occasion a total of 52 mg. of acetyl- β -methylcholine was given in divided doses. Following this, rather alarming symptoms developed, associated with transient cardiac standstill, and simultaneously the attack stopped.

CASE 5.—A 19-year-old student was observed in November, 1933, complaining of pain in the left chest of 2 days' duration. Physical examination revealed no abnormality of the cardiovascular system. Blood pressure was 120/70. During attacks the heart rate was 200 to 220 per minute and electrocardiogram showed paroxysmal auricular tachycardia. Two attacks were relieved by pressure on the eyeballs. This measure, as well as pressure on the carotid sinus, was ineffective in a third attack. Administration of 2 drams of syrup of ipecac abolished the attack in 18 minutes. Ipecac has been used in subsequent attacks, with relief.

CASE 6.—A 23-year-old man entered the hospital in November, 1932, with the complaint of attacks of forceful, rapid heart beat during the past 6 years. These attacks were precipitated mainly by nervous strain and usually started with a sensation as if the heart was "flopping over." The rate became rapid, "about 200." Simultaneously there was a sensation of light-headedness, of vertigo, of a lump in the throat and of choking. The attacks ended abruptly after 6 to 12 hours; in some he experienced precordial pain, radiating to the back. Physical examination was negative. The patient was not observed in an attack while in the hospital. Between

attacks the electrocardiogram was normal except for the diphasic T_3 . The clinical diagnosis of paroxysmal auricular tachycardia was made and the patient was advised to take 1 or 2 drams of syrup of ipecac in case of an attack. During the following 14 months he had 6 attacks, each of which was promptly relieved within one-half to three-quarters of an hour after taking ipecac.

CASE 7.—A 29-year-old technician was observed between 1931 and 1934. He had a history of rheumatic fever, and complained of attacks of palpitation, rapid heart action and precordial distress. Physical examination revealed an aortic insufficiency with enlargement of the heart. The blood pressure was 160 to 170 over 70 to 80 mm. Hg. The blood serologic tests were negative. Electrocardiograms showed paroxysmal auricular tachycardia. In March, 1931, the patient developed an attack of paroxysmal auricular tachycardia with a rate of 180 to 210, which lasted for several days. Various physical manipulations, as well as the administration of quinidine, gave no relief. Oral administration of 2 drams of syrup of ipecac subsequently induced vomiting in 30 minutes and simultaneously normal sinus rhythm was reestablished.

In July, 1935, the patient entered the hospital with a similar attack, which had lasted over 12 hours. Fifteen minutes after the administration of 1 dram of syrup of ipecac he became nauseated and vomited. Simultaneously the heart rate slowed down for a few minutes, but thereafter the tachycardia returned. About 15 to 17 minutes after another dram of syrup of ipecac, the patient vomited again, and simultaneously normal sinus rhythm returned. An electrocardiogram revealed sinus rhythm of 76 with premature auricular and ventricular beats. QRS was 0.12 second; $P-R$ 0.28 second.

CASE 8.—A 20-year-old girl entered the hospital on December 15, 1931, complaining of attacks of palpitation and dyspnea. For 12 years she was known to have rheumatic heart disease. During the past 2 years she had experienced attacks of rapid heart rate associated with palpitation, dyspnea and a sensation of faintness. The heart was enlarged. There was a double murmur over the aortic area. The blood pressure was 150/0 mm. Hg. The blood serologic tests were negative. Among the various manipulations, pressure over the carotid sinus was the only one to relieve the attack. On two occasions the attacks were relieved 17 and 22 minutes, respectively, after the oral administration of 2 drams of syrup of ipecac. Relief coincided with the onset of severe nausea and retching.

CASE 9.—A 52-year-old laborer entered the hospital on January 17, 1932, with the history of shortness of breath of 9 months' duration and attacks of palpitation for 3 months. The heart was enlarged to the left and to the right. No evidence of valvular lesions was elicited. The arterial pressure was 180/100. He was observed in two attacks, which were revealed by electrocardiogram to be paroxysmal auricular tachycardia. Both attacks were relieved one-half to 1 hour after the administration of 2 drams of syrup of ipecac. Following this relief the electrocardiogram showed sinus rhythm with left ventricular preponderance. The rate was 94, the $P-R$ interval 0.16 second and the QRS interval 0.07 second. The T waves were upright in all leads.

CASE 10.—A 48-year-old housewife suffered from pernicious anemia associated with attacks of palpitation. On physical examination the heart was normal; the blood pressure was 110/80 mm. Hg. The electrocardiogram indicated that the attacks were paroxysmal auricular tachycardia. The patient was observed in one of her attacks, which lasted for 4 hours. She became nauseated and vomited 38 minutes after the oral administration of 2 drams of ipecac. At the same time the heart rate dropped from between 200 and 210 to from 80 to 84 and the patient was relieved.

CASE 11.—A 19-year-old nurse was observed in May, 1931. She complained of attacks of precordial distress and palpitation. Physical examination was negative. During the attacks the heart rate was over 200 per minute. Twelve minutes following the administration of 2 drams of syrup of ipecac the patient vomited and the heart rate dropped to 64, later rising to from 80 to 84 per minute. Four subsequent attacks were relieved by ipecac.

The Relation of the Irritability of the Vagal Reflexes to the Principle of Treatment of Paroxysmal Auricular Tachycardia. Clinical and experimental evidence indicates that much variation exists in the tonus of the individual reflexes of the autonomic nervous system, both in health and in disease. The irritability and the motor effects of the same autonomic reflex exhibit considerable variation in normal persons. Increased motor tonus within the sympathetic nervous system often depends on hyperactivity of individual reflexes of the autonomic nervous system, rather than of the entire system.¹ In analyzing certain clinical manifestations of the hyperactive carotid sinus reflex, it has been stated: "What we consider as the vagal or other medullary center is, therefore, a condensed and busy relay station with some constant, but also with numerous continuously changing activities of sensory and motor connections. Some of these active reflexes are innate; some develop with the evolution of the body; others are the result of training; and still others develop with disease."⁷

Increased cardiac vagal tone depends on increased activity of vagal reflexes, rather than on local stimulation of the vagal motor nerve endings. The sensory-vagal reflexes influencing the heart are numerous. Patients have been observed in whom temporary cardiac standstill could be induced by a slight degree of stimulation of afferent endings of the intercarotid nerve within the carotid sinus, of trigeminal nerve endings within the orbit, of afferent vagal nerves in the throat, esophagus or stomach, or of afferent pleural nerves.^{1,6,7,8} In these patients hyperactivity of one of these autonomic reflexes was usually associated with a normal state of other reflexes. In a study of the carotid sinus reflexes it was also observed that even within the group of subjects with "normal responses" marked variations existed in the degree of cardiac slowing which could be induced by stimulation of the sinus. In some subjects, stimulation failed to induce inhibitory influence on the heart; in others, the slowing was slight and transient; and in still others it was marked. Moreover, the response of one carotid-sinus frequently differed from that of the other.^{1,7} A similar variation in the reflex response exists in the behavior of the oculovagal reflex (Aschner-Dagnini phenomenon).⁶

Another instance of variation in vagal reflexes can be found in the behavior of vomiting. It is known that vomiting is always a reflex act, depending on peripheral stimulation of the medullary vagal

centers, on a primary increase of the excitability of these centers, or on a combination of these two factors.^{2a} The act of vomiting is often associated with hyperactivity of a number of vagal and parasympathetic reflex manifestations. The extent of these vagal manifestations, however, varies considerable depending not only on the etiology and mechanism of various types of vomiting, but also on the innate character of the autonomic nervous system of the subject. Both in animals^{2a,2c} and in man,^{1,6} the same type of peripheral and central stimulation of the vagus system produces various degrees of increase in the cardiac vagal tonus. Some of the centrally acting vagal stimulants, such as morphine, apomorphine and medullary anoxia, have abolished attacks of paroxysmal auricular tachycardia in some but not in other subjects. In a study of vasomotor collapse induced with sodium nitrite, it has been observed that in normal subjects cerebral ischemia induces varying degrees of cardiac inhibition. In some individuals no vagal inhibition was observed.⁹ Thus central vagal response to anoxia also shows marked individual variations. These considerations, as well as the experience we have gained with the use of central and peripheral emetics in the treatment of paroxysmal auricular tachycardia, indicate that the degree of cardiac vagal inhibition does not necessarily parallel the vagal action on the gastro-intestinal canal. One type of emetic may be capable of stopping an attack of paroxysmal auricular tachycardia, while another is ineffective.

Central vagal inhibition of anoxemic origin plays a rôle in the spontaneous cessation of the attacks. Thus we have had the opportunity to observe a 37-year-old patient without organic heart disease whose attacks during the past 25 years never lasted longer than from 2 to 8 minutes. With the onset of an attack her normally low arterial pressure of 90 to 100 mm. Hg systolic and 64 to 70 mm. Hg diastolic rapidly fell to between 40 and 60 mm. The attack of tachycardia of from 150 to 160 per minute was associated with dizziness, weakness, dimness of vision and profuse perspiration. When these manifestations became pronounced, and the blood pressure could barely be measured, she experienced sudden slow palpitation for from 10 to 20 seconds. The heart rate simultaneously dropped to from 30 to 40 per minute and thereafter a normal sinus rhythm of 80 to 90 per minute became reëstablished. Here we are dealing, then, with a self-regulatory therapeutic function of the body. The tachycardia results in reduction of the cardiac output, which, in turn, leads to medullary ischemia (vasovagal syncope),⁹ causing central vagal stimulation and return of the sinus rhythm.

These examples clearly indicate, then, that the sensory cardio-vagal reflex nerve endings and their central synapses can be stimulated in a number of ways. The effectiveness of the stimulation depends, among other factors, on the normal "activity" and "tonus" of the specific reflex in the given case. If a reflex is

not active, stimulation may be ineffective. In a healthy person, some of the vagal reflexes may be ineffective, others normally active, while others may be relatively hyperactive. Thus in an individual with an active carotid sinus reflex, stimulation of the sinus will be an effective measure for inducing asystole, while stimulation of other afferent pathways of the vagus may be entirely without effect. We have demonstrated that stimulation of the carotid sinus will abolish attacks in one group of patients with paroxysmal auricular tachycardia, but it will remain ineffective in another group.⁷ The more developed the carotid sinus-cardio-vagal reflex is, the more effective is the stimulation. This can be illustrated by a case in which there was the unusual coexistence of a hyperactive carotid sinus reflex and paroxysmal auricular tachycardia. Through the courtesy of Dr. H. L. Blumgart we had the opportunity to observe a 57-year-old patient who, during the past 20 to 25 years, has had attacks of palpitation, in recent years followed by giddiness and finally by syncope associated with rapid heart rate. In the beginning the attacks occurred once in 6 months and lasted for only 15 minutes, but they have gradually increased in frequency and in duration. During one of the attacks observed, the cardiac rate was 200 per minute. The rhythm was regular. The heart was normal in size. The arteries were sclerosed. There was no venous engorgement, cyanosis or peripheral edema. Pressure on either carotid sinus, but especially on the right, reduced the rate to 80. Continued pressure on the right sinus finally resulted in complete asystole, and in a rapid fall of the blood pressure to 80 mm. Hg. The patient felt faint and dizzy and his respirations became slow. Thus in this patient, as a result of the coexistence of paroxysmal tachycardia and hyperactive carotid sinus reflex, it was possible to change the cardiac rate of 200 to a state of asystole.

The marked individual variations in reflex excitability of the sensory-cardio-vagal reflexes are, in our opinion, to a large extent responsible for the variability of response to the different measures advocated in the past for the treatment of paroxysmal auricular tachycardia. In view of the variations in the response of vagal reflexes, as well as in the central synapses, such variations in response are inevitable. As we do not possess methods to determine which type of sensory-vagal reflex is most effective for increasing the cardio-vagal tone in a given case, for practical purposes it remains essential to test the efficacy of several types of peripheral or central vagal stimulation.

Summary. 1. Ipecac is a useful agent in the treatment of paroxysmal auricular tachycardia.

2. In 11 cases attacks were relieved following the oral administration of doses of from 4 to 32 cc. (1 to 8 drams) of syrup of ipecac.

3. The pharmacologic principle underlying this method of treatment and the considerations to be observed in its application are described.

4. The relation of the physiologic state of the autonomic nervous system, and particularly of the sensory-vagal reflexes, to the effective treatment of paroxysmal auricular tachycardia is discussed. The more powerful the vagal stimulus applied and the more increased the tonus of the specific reflex, the greater is the probability of therapeutic success.

5. The pronounced variations in the tonus and in the irritability of the various cardiac inhibitory reflexes are the basic cause underlying the variability of effectiveness of measures used in the treatment of paroxysmal auricular tachycardia.

REFERENCES.

- (1.) Ferris, E. B., Jr., Capps, R. B., and Weiss, S.: *Medicine*, 14, 377, 1935. (2.) Hatcher, R. A., and Weiss, S.: (a) *J. Pharm. and Exp. Therap.*, 22, 139, 147, 158, 1923; (b) *Ibid.*, p. 181; (c) *Arch. Int. Med.*, 29, 690, 1922; *J. Pharm. and Exp. Therap.*, 32, 37, 1927. (3.) Mackenzie, J.: (a) *Diseases of the Heart*, Oxford Med. Pub., London, Henry Frowde, and Hodder & Stoughton, p. 253, 1918; (b) *Loc. cit.*, p. 438. (4.) Schilder, G.: *München. med. Wehnschr.*, 81, 1297, 1934. (5.) Starr, I., Jr.: *AM. J. MED. SCI.*, 186, 330, 1933; 191, 210, 1936. (6.) Weiss, S.: *Syneope and Related Syndromes*, in Christian, H. A., and Mackenzie, J.: *Oxford Medicine*. London, Oxford Univ. Press, 2, 250, 1935, Chap. 8-A. (7.) Weiss, S., and Baker, J. P.: *Medicine*, 12, 297, 1933. (8.) Weiss, S., and Ferris, E. B., Jr.: *Arch. Int. Med.*, 54, 931, 1934. (9.) Weiss, S., Wilkins, R. W., and Haynes, F. W.: *J. Clin. Invest. Invest.*, 16, 73, 1937. (10.) White, P. D.: *Heart Disease*, New York, The Macmillan Company, p. 639, 1931.

ADULT SCURVY; STUDY OF THE URINARY OUTPUT OF CEVITAMIC ACID.*

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SINCE 1928, great strides have been made in the purification, isolation, and synthesis of vitamin C.

Szent-Gyorgi's^{23a,b} original discovery of a strongly reducing substance in the adrenal cortex of oxen, as well as in oranges and cabbages, was really the forerunner of the present researches. Szent-Gyorgi extracted this reducing substance from the adrenal and regarded it as an acid of the hexuronic series. Tillmans, *et al.*,^{24,25} trying to differentiate between true and artificial lemon juice, found that 2 to 6 dichlorophenol-indophenol was decolorized only by true lemon juice. They subsequently made the suggestion that the distribution of Szent-Gyorgi's hexuronic acid in nature coincided with the distribution of vitamin C. Szent-Gyorgi and

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Svirbely^{22a,b} then succeeded in curing guinea-pigs of scurvy with hexuronic acid. Finding that hexuronic acid also reduced dichlorophenol-indophenol prompted them to suggest that the acid was identical with the reducing substance found by Tillmans in lemon juice. King and Waugh^{14a,b} stated that they obtained a crystalline substance from lemon juice which showed antiscorbutic properties and was similar in chemical and physical properties to hexuronic acid. The final establishment of hexuronic acid as vitamin C and the synthesis of the compound was established first by Haworth¹⁰ and secondly by Reichstein, Grussner, and Oppenauer.¹⁸

In the last 3 years much work^{5,13,17} has been done on the urinary excretion of vitamin C, following Harris, Ray, and Ward's⁸ studies in 1933.

In a person whose diet has been adequate in vitamin C, the quantity of urinary excretion of the vitamin, or as it is now called, cevitamic acid, is constant from day to day and averages about 15 to 33 mg. daily; Ahmad² 23 to 35 mg., Hawley⁹ 15 to 28 mg., Harris and Ray⁸ 30 to 33 mg. The greater the intake of vitamin C, the greater is the urinary excretion. If a test dose of 600 mg. is given, there is considerable rise in excretion for the next 24 hours. If excessive amounts of vitamin are given for a considerable length of time, most of the excess is stored chiefly in the adrenals, pituitary, and liver, the remainder excreted until a point of complete "saturation" is reached. When this occurs, about 80% of all additionally ingested vitamin C is excreted, the fate of the other 20% being unknown. Thus the amount of test dose of 600 mg. excreted in a given patient at a given time depends upon the degree of saturation. If the excess intake is stopped, the urinary output falls to normal levels. If the patient is now placed on a vitamin C-free diet, he continues to excrete normal amounts for a time. In other words, the body slowly gives up its store. Eventually, if the patient is continued on a vitamin C-free diet, the urinary output will fall to very low levels until, with depletion of the reserve, the excretion becomes negligible.

Johnson and Zilva¹³ gave a somewhat different definition of saturation. They showed that in patients with a previous history of low vitamin C intake there is an initial level below normal in urinary excretion of the vitamin. The response to the test dose is not very great and not until several days of high intake have elapsed does excretion begin to rise. And, finally, not until an additional number of days passes, does it attain a constant level. These authors considered a patient saturated when he reached this constant level. The length of time required to reach complete saturation is greater in people with a background of low vitamin C intake than in normal persons on the same dosage.

Youmans and his co-workers²⁹ have suggested that complete saturation does not indicate a normal degree of vitamin C storage

but rather an artificial state created by excessive intake. It seems fair to assume, however, that the excretion of about 30% of the test dose in a patient indicates an approximately normal state.

Case Report. M. R., a female, aged about 60, was admitted to this hospital on February 16, 1936, complaining of painful bluish areas on the surface of the body, especially the legs, of 10 days' duration. Her family history was non-contributory. She had had her menopause 20 years ago. There had been a previous admission 6 months before with complaints of fever and a generalized eruption. She remained in the hospital for 3 weeks, during which time her symptoms cleared up, and complete roentgenologic, serologic, and bacteriologic studies failed to reveal the nature of her illness. She then remained apparently well until 10 days prior to the present admission when she began to develop painful ecchymotic areas on the knees, thighs and gluteal regions, associated with generalized muscle tenderness. No history of trauma could be elicited. Anorexia appeared. Several days after the onset she had a spontaneous nose bleed of short duration. The next day she developed blueness over one eye. For the week prior to admission there was swelling of the gums with tenderness, but no bleeding. There was no melana, hematuria, or hemoptysis. Further questioning revealed the fact that she lived alone. For the past year her food intake had consisted chiefly of dairy products and soups; she had taken practically no vegetables, fruits, or meats.

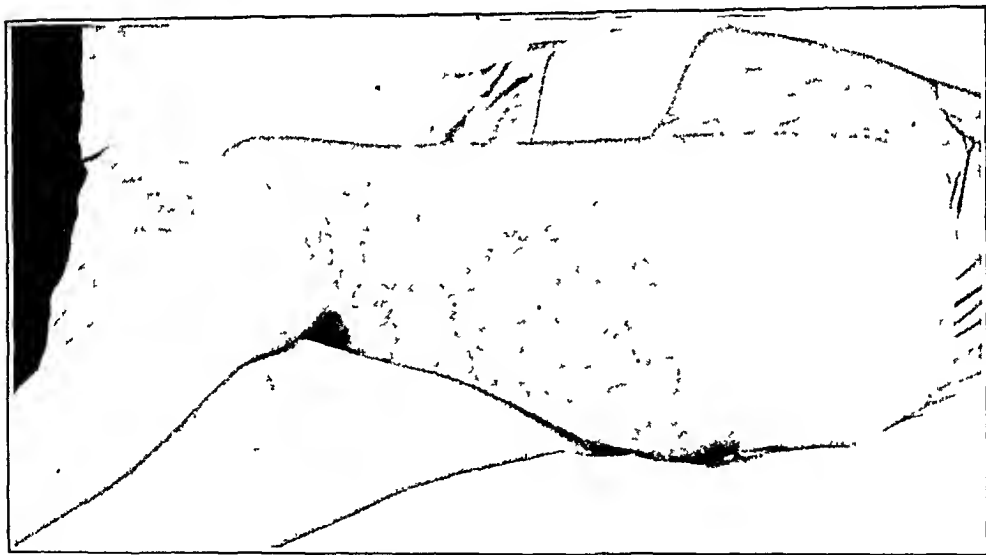


FIG. 1.—Subcutaneous hematoma on thigh.

Physical Examination. Temperature, pulse and respirations were normal. She was an elderly woman in no apparent distress other than from pain in the lower extremities. Her mental condition indicated senile changes. The skin was dry, scaly, and atrophic. The lips and nail beds were slightly cyanosed. Numerous small purpuric areas were present on the skin surface. There were a number of large hematomata on both lower extremities, especially the left, where one large patch covered the entire inner and under aspect of the thigh (Fig. 1), and another the inner calf (Fig. 2). A similar lesion was located above the symphysis pubis. These were hard, brawny, and extremely tender. The retinae were normal. All teeth were absent

except the stumps of the two lower central incisors. The gums were normal, except around these two teeth where they were swollen and hemorrhagic. A small reddish spot was present on the right posterior pharyngeal wall. Examination of the heart, lungs, abdomen, and pelvis was essentially negative. There was no glandular enlargement. A Parkinsonian tremor was present.

Laboratory Data. Red blood cells 2,500,000 per c.mm., hemoglobin 58% (Sahli); white blood cells 3100, neutrophils 66%, unsegmented 2, lymphs. 26, monos 6%; smear showed anisocytosis and slight polychromatophilia; platelets 186,000 per c.mm.; reticulocytes 2.6%; coagulation time $4\frac{1}{2}$ minutes; clot retraction normal; bleeding time 3 minutes. The tourniquet test was markedly positive. The urine was negative. Blood Wassermann test was negative. Blood volume by Rowntree method 4235 cc. (103 cc. per kilo); plasma volume 3078 (75 cc. per kilo). Stools were negative for occult blood. Electrocardiogram was normal. Roentgen-rays of the chest and long bones were normal.



FIG. 2.—Subcutaneous hematoma on thigh and calf.

Course. The laboratory data presented ruled out the primary blood dyscrasias. On the basis of the history and physical findings, together with the negative results of the blood examinations, the diagnosis of scurvy was made. After several days of observation and control studies, she was placed on a régime high in vitamin C content. This consisted partially of orange juice (containing 18 mg. of cevitamic acid per ounce) and partially of cevitamic acid (Hoffman-La Roche) (Chart I). The patient's general condition promptly began to improve; she became brighter, more alert, and interested in her surroundings. There were no fresh hematomata or purpuric spots: The old ones almost immediately began to clear up, and gradually disappeared. The gum lesions also improved considerably. Her red blood count rose to 3,650,000 per c.mm., and hemoglobin to 73%; the leukopenia persisted. The response to tourniquet test gradually diminished until it was only very slightly positive. By the tenth day of treatment she was entirely cured, but remained for 7 additional days of study.

As soon as the diagnosis was established, studies of the urinary output of cevitamic acid were begun. The method of urinary titration used was Bireh, Harris and Ray's⁵ modification of Tillman's determination. The urine was collected from 8 P.M. to 8 P.M. in dark colored bottles to which 10 cc. of glacial acetic acid had been previously added. The dye (2 to 6 dichlorophenol-indophenol) was standardized every 2 to 3 days against a known amount of

cevitamic acid. The urine was titrated 3 to 4 hours after voiding. Five-hundredths of a gram of dye were dissolved in a small amount of boiling water, and more boiling water up to 25 cc. was added. The resulting solution was filtered. A solution of accurately weighed cevitamic acid was titrated with the dye until the solution turned pink, thus standardizing the dye, 0.05 cc. of which usually equalled about 0.025 mg. of cevitamic acid. For titrating urine, 0.05 cc. of dye were placed in a test tube to which about 2 cc. of water were added. The dye was titrated with urine which was acid to litmus paper, until the red color of the dye changed to the color of the urine, a little of the urine in another test tube being used for comparison. The 24-hour excretion of the vitamin could then be calculated.

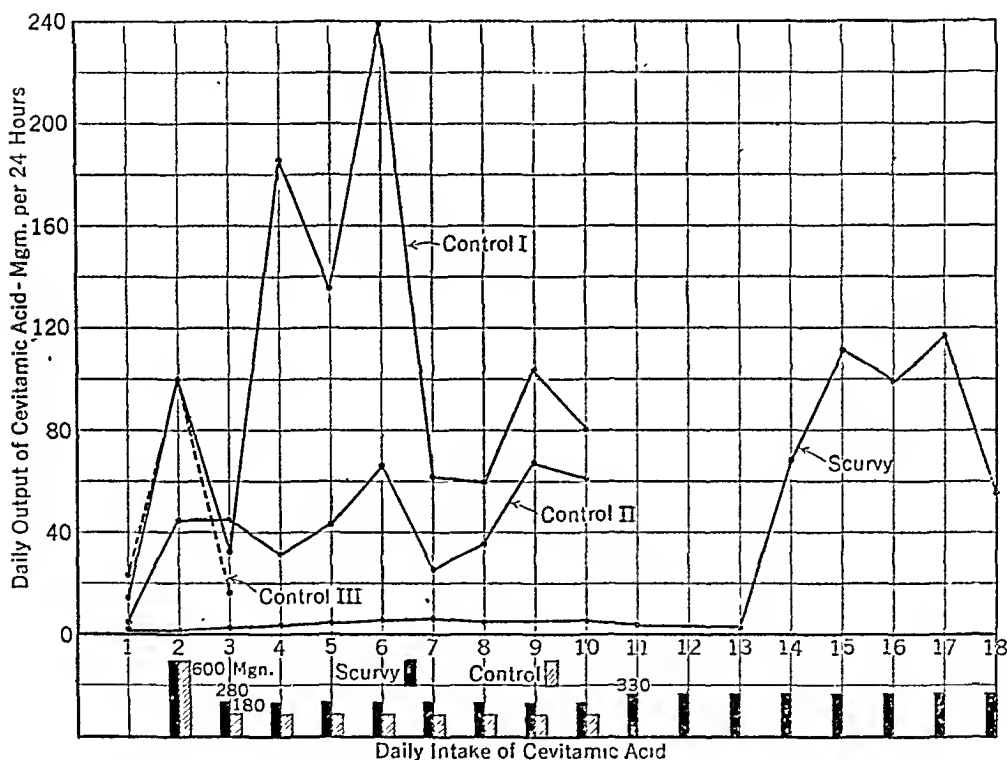


CHART I.—Daily urinary vitamin C excretion of case of scurvy and 3 controls.

The results are tabulated in Chart I. For the first 24 hours, on a control diet, the excretion was 1.75 mg. She then received a test dose of 600 mg. of cevitamic acid, given orally, followed by daily doses of 280 mg. for 8 days, and then 330 mg. for 8 more days. Despite these large doses, the daily excretion for 24 hours remained below 6.5 mg. On the twelfth day, a rise in the curve took place and higher levels of excretion were then maintained. At the time the rise occurred, the patient was symptomatically cured, and insisted upon leaving the hospital a few days later, thus preventing further studies which would have been desirable.

For contrast, the chart shows the output curves in a few controls. Curve I, of a case of pernicious anemia, shows an initial output of 14.4 mg. The test dose of 600 mg. resulted in an excretion of 100 mg. Thereafter, on 180 mg. daily, a high level of excretion was obtained. Curve II, of a case of inactive rheumatic fever, showed lower levels of excretion, but much higher than those of the scurvy patient. The short Curve III shows the response to the test dose of 600 mg. of one of us (A. N.).

Comment. From a diagnostic viewpoint, several features deserve comment. The hematomata were characteristic of scurvy in that they were hard, brawny, and extremely tender; this is known as "scurvy sclerosis".^{11,15} The presence of hemorrhages in only those portions of the gums surrounding teeth is extremely characteristic, being stressed by such leading authors on scurvy as Hess,¹¹ Selle and Rosenberg,²⁰ Schultz.^{19b} Roentgenologic changes in the bones and joints, while frequently seen in childhood scurvy, are rarely seen in the adult form.

It is well established now, since Schultz^{19a} in 1933 first cured a case of scurvy with intravenous injections of cevitamic acid, that the latter substance alone, given orally or intravenously, is efficacious in curing the disease. This was confirmed by Neumann,¹⁶ Brugsch,⁶ Wentzler,²⁶ Goettsch,⁷ Bell,⁴ and Svensgaard²¹ in infants and recently by Wright and Lillienfeld²³ and Bauke³ in adults.

Discussion. In reviewing the literature, we have found only 4 cases of adult scurvy where similar studies were made. Wood,²⁷ in 1935, reported a case in which the initial output was zero, compared to 53 mg. in a control; the output after the test dose of 600 mg. was 1.7 mg. in the scorbutic patient, compared to 231 mg. for the control. On 80 mg. a day, the patient showed clinical improvement, and was discharged after 12 days, during which time there was no vitamin C excretion in the urine.

Since our studies were completed, Schultz^{19b} has reported 3 cases of scurvy in which very complete urinary studies were made. His results differ from ours in that his initial levels were either normal or somewhat subnormal though, in general, they ranged below his controls. Schultz, himself, remarks that his initial levels are surprisingly high. He gave his patients daily doses of 300 mg. intravenously, 600 mg. intravenously, and 600 mg. orally, respectively. His curves, showing the response to large doses of cevitamic acid, are very similar to ours and show considerable evidence of unsaturation when compared to his controls. The 3 cases required a total of 9.5, 7, and 14.4 gm. of cevitamic acid over a period of 5, 2 and 3 weeks before "saturation" was reached, using the criteria of Johnson and Zilva.¹³ In 6 controls, however, similar urinary responses were obtained after 5 to 7 days on 600 mg. daily. In all 3 cases, marked clinical improvement was noticed after 2 to 3 days of high vitamin C therapy.

Harris and Ray¹⁷ found subnormal excretion in two scorbutic children with no appreciable increase in output after the test dose. After cure had been effected, excretion was normal, the test dose then resulting in excretion of a large percentage of the intake.

In our scurvy case there is obvious evidence of tremendous unsaturation, so much so that with an intake of almost 3.7 gm. of cevitamic acid in the first 13 days, she practically excreted none. During this time her tissues were gradually storing the vitamin, so that on the 12th day she excreted about 18% of her intake. In other words, she was now beginning to respond like a normal person. This she continued to do for the remaining 5 days of the study. Control I, however, showed a normal initial level, excreted 100 mg. of the test dose, indicating a normal degree of "saturation," and then continued to excrete a high percentage of the intake. In Control II, however, there was an initial level of 6, with a response of only 45 to the test dose. Excretion following the oral intake of 180 mg. daily was never higher than 67. This curve is lower than that of Control I, although much higher than of our case of scurvy. This patient was a cardiac who had long been on restricted diets. Abbasy, Harris, and Ray.¹ in doing excretion studies on random cases in a large children's hospital, found evidence of considerable unsaturation in many. In reviewing the records they found these to be cases where for one reason or another there had previously been a low vitamin C intake. They used these results to further the concept of subclinical scurvy, first introduced by Hess and Fish¹² in 1914, interest in which has been stimulated in recent years by the advances in the field of vitamin C excretion. This subject is beyond the realm of our paper.

Summary. A case of adult scurvy is presented. The study of the urinary excretion of vitamin C showed evidence of tremendous bodily unsaturation of the vitamin when compared to values obtained by other authors for normal individuals and to our own controls.

We wish to express appreciation to Dr. I. W. Held for his constant interest, and to Dr. H. Schwarz who stimulated our interest in the subject of vitamin C excretion in general.

REFERENCES.

- (1.) Abbasy, M. A., Harris, L. J., Ray, S. N., and Marrack, J. R.: *Lancet* 2, 1399, 1935. (2.) Ahmad, B.: *Biochem. J.*, 29, 275, 1935. (3.) Bauke, E. E.: *München. med. Wehnsehr.*, 81, 1240, 1934. (4.) Bell, A. D.: *Lancet* 1, 547, 1935. (5.) Birch, T. W.: Harris, L. J., and Ray, S. N.: *Biochem. J.*, 27, 590, 1933. (6.) Brugsch, H.: *Deutsch. med. Wehnsehr.* 60, 1202, 1934. (7.) Goettsch, E.: *Am. J. Dis. Child.*, 49, 1441, 1935. (8.) Harris, L. J., Ray, S. N., and Ward, A.: *Biochem. J.*, 27, 2011, 1933. (9.) Hawley, E., Stephens, D. J., and Anderson, G.: *J. Nutrition*, 11, 135, 1936. (10.) Haworth, W. N.: *J. Soc. Chem. Ind.*, 52, 482, 1933. (11.) Hess, A. F.: *Scurvy, Past and Present*, J. B. Lippincott & Co., Philadelphia, 1920. (12.) Hess, A. F., and Fish, M.: *Am. J. Dis. Child.*, 8, 385, 1914. (13.) Johnson, S. W., and Zilva, S.: *Biochem. J.*, 28, 1393, 1934. (14.) King, C. G., and Waugh, W. A.: (a) *J. Biol. Chem.*, 97, 325, 1932; (b) *Science*, 75, 357, 1933. (15.) Meulengracht, E.: *Acta med. Scand.*, 67, 43, 1927. (16.) Neuman, U.: *Deutsch. med. Wehnsehr.*,

- 60, 1203, 1934. (17.) Ray, S. N., and Harris, L. J.: *Lancet*, 1, 71, 1935. (18.) Reichstein, T., Grussner, A., and Oppenauer, R.: *Helv. Chim. Acta*, 16, 561, 1933. (19.) Schultzer, P.: (a) *Acta med. Scand.*, 86, 317, 1936; (b) *Lancet*, 2, 589, 1933. (20.) Selle, V., and Rosenberg, M.: *Eigeb. der Inner. Med.*, 19, 31, 1921. (21.) Svensgaard, E.: *Lancet*, 1, 22, 1934. (22.) Svirebely, J. L., and Szent-Gyorgi, A.: (a) *Biochem. J.*, 26, 865, 1932; (b) 27, 279, 1933. (23.) Szent-Gyorgi, A.: (a) *Nature*, 119, 782, 1927; (b) *Biochem. J.*, 22, 1387, 1928. (24.) Tillmans, J., and Hirsch, P.: *Biochem. Zeitschr.*, 250, 312, 1932. (25.) Tillmans, J., Hirsch, P., and Jackisch, J.: *Zeits. f. Untersuch. d. Lebensm.*, 63, 241, 1932. (26.) Wentzler, E.: *Monatschr. f. Kinderh.*, 59, 451, 1934. (27.) Wood, P.: *Lancet*, 2, 1405, 1935. (28.) Wright, I. S., and Lillienfeld, A.: *Arch. Int. Med.*, 57, 241, 1936. (29.) Youmans, J. B., Corlette, M. B., Akeroyd, J. H., and Frank, H.: *AM. J. MED. SCI.*, 191, 318, 1936.

FEBRILE ALBUMINURIA.

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THE production of artificial fever, in addition to its value in therapy, offers a rather unusual opportunity to study the physiology of the body in the presence of an uncomplicated temperature elevation. Bierman and Fishberg¹ have recently contributed a great deal of our knowledge of this subject. I have been particularly interested in the relation of fever to albumin in the urine, a matter which these authors did not consider, and have had the opportunity to study from this point of view 40 patients receiving fever therapy at this hospital.

The term "febrile albuminuria" was applied by Gerhardt,⁴ in 1868, to describe the increase in urinary proteins during elevation of the body temperature, although first mentioned by Martin-Solon⁷ some 30 years before. Since Gerhardt's time the term has been used quite extensively, but whether or not fever *per se* actually causes an increase in the amount of urinary protein has not been determined, judging from a survey of the medical literature.

All modern textbooks of medicine call attention to the phenomenon but opinions vary as to the real cause. A. M. Fishberg, for example, says: "Albuminuria may occur in almost any febrile state, but is most common when the fever is very high and protracted Anatomically, cloudy swelling of the epithelium, particularly of the convoluted tubules, is found. Not uncommonly, there is also fatty change of varying degree, though rarely marked. The albuminuria is generally attributed to these changes in the renal epithelia. It should be mentioned, however, that similar cloudy swelling and fatty change may be found where there was no albuminuria during life. . . . *It has not been proved that the renal lesions and albuminuria are due directly to the elevation of temperature.* [My italics.] Against such a view is the fact that fever may be very high for a considerable time without accompanying albumin-

uria. Injury to the renal cells by circulating toxic substances would seem more probable, for similar renal lesions and albuminuria occur in various afebrile toxemias and chemical poisons."

Opposed to this Osler and McCrae⁸ state: "Pyrexia, by whatever cause produced, may cause slight albuminuria, due to slight changes in the glomeruli induced by fever, such as cloudy swelling which cannot be regarded as an organic lesion. It is extremely common, occurring in pneumonia, diphtheria, typhoid fever, malaria, especially the æstivo-autumnal type, and in acute tonsillitis. The amount is slight, and it usually disappears with the cessation of fever."

The majority of other authors believe with Fishberg that the albuminuria is a manifestation of the accompanying infection and toxemia rather than of the fever itself. The difficulties, of course, have been that fever is almost always caused by an infectious process, and that the probable causative factors have never existed alone. However, in fever therapy one has a marked elevation of body temperature maintained for several hours without an accompanying infection, a *true uncomplicated fever*. Conditions are ideal for the study of febrile albuminuria.

The method of study used was as follows: Patients being treated in this department, who suffered from general paresis, atrophic arthritis, gonorrheal arthritis and chorea, were used. All had a blood-urea nitrogen within normal limits, a normal Mosenthal concentration test and several negative examinations of the urine for albumin. Fever was induced by means of the Kettering hypertherm and an average temperature of 105° to 106° F. was maintained for 4 to 6 hours. A specimen of urine was obtained before the febrile period; a second specimen was collected after fever had reached its height and had been maintained for several hours; the third specimen was the first urine voided after the temperature had fallen to normal, usually 2 to 3 hours after removal from the fever cabinet. These urines were then examined as to specific gravity, reaction to litmus paper, and for gross albumin by the sulphosalicylic acid reagent. The exact amount of urinary albumin was determined by the quantitative sedimentation method of Shevky and Stafford⁹ in which the albumin is precipitated by Tsuchiya's reagent, centrifuged in a specially designed tube and the volume of the precipitate read directly on a scale. Results are shown in Table 1.

In 95% of the subjects the pre-fever urine albumin was below 0.03% and 80% presented a figure below 0.02%. The urine albumin exceed 0.04% in only 1 patient. These are normal values and offer better proof of absence of renal disease in the group than the blood-urea nitrogen and the Mosenthal test.

During the febrile period 22.5% of cases showed a decrease in albumin with fever while 77.5% (31 of the 40 patients) had an increase in the level of urine albumin. This increase was very

TABLE 1.—URINE FINDINGS BEFORE, DURING AND AFTER FEVER.

No.	Name.	Sp. gr.	Reaction.	Gross alb.	Quant. alb., per cent.
1	W. M.	b.f. 1.020	Acid	Negative	0.007
		d.f. 1.015	Acid	Negative	0.018
		a.f. 1.008	Acid	Negative	0.007
2	C. S.	b.f. 1.010	Acid	Negative	0.007
		d.f. 1.017	Acid	Cloud	0.081
		a.f. 1.020	Acid	Negative	0.014
3	F. S.	b.f. 1.022	Alkaline	Negative	0.017
		d.f. 1.024	Acid	Trace	0.030
		a.f. 1.010	Alkaline	Negative	0.014
4	H. S.	b.f. 1.022	Alkaline	Negative	0.029
		d.f. 1.026	Alkaline	Cloud	0.054
		a.f. 1.022	Alkaline	Cloud	0.075
5	B. W.	b.f. 1.020	Acid	Negative	0.010
		d.f. 1.022	Acid	Trace	0.030
		a.f. 1.018	Acid	Negative	0.015
6	C. E.	b.f. 1.016	Acid	Negative	0.015
		d.f. 1.020	Alkaline	Negative	0.054
		a.f. 1.022	Alkaline	Negative	0.020
7	J. T.	b.f. 1.012	Acid	Negative	0.010
		d.f. 1.012	Acid	Trace	0.054
		a.f. 1.016	Acid	Negative	0.007
8	E. G.	b.f. 1.012	Alkaline	Negative	0.007
		d.f. 1.020	Alkaline	Negative	0.010
		a.f. 1.020	Acid	Negative	0.020
9	C. N.	b.f. 1.018	Alkaline	Negative	0.010
		d.f. 1.025	Alkaline	Negative	0.016
		a.f. 1.010	Alkaline	Negative	0.007
10	M. C.	b.f. 1.022	Alkaline	Negative	0.002
		d.f. 1.022	Alkaline	Negative	0.003
		a.f. 1.010	Acid	Negative	0.018
11	M. J.	b.f. 1.020	Acid	Negative	0.014
		d.f. 1.020	Alkaline	Cloud	0.065
		a.f. 1.030	Acid	Cloud	0.097
12	J. B.	b.f. 1.017	Alkaline	Negative	0.018
		d.f. 1.022	Alkaline	Negative	0.072
		a.f. 1.025	Alkaline	Negative	0.065
13	A. H.	b.f. 1.024	Acid	Negative	0.017
		d.f. 1.036	Alkaline	Negative	0.014
		a.f. 1.036	Acid	Negative	0.049
14	C. J.	b.f. 1.020	Acid	Negative	0.007
		d.f. 1.026	Acid	Negative	0.004
		a.f. 1.026	Acid	Negative	0.005
15	T. D.	b.f. 1.030	Acid	Negative	0.072
		d.f. 1.030	Acid	Negative	0.076
		a.f. 1.025	Alkaline	Negative	0.014
16	A. D.	b.f. 1.020	Acid	Negative	0.025
		d.f. 1.018	Alkaline	Negative	0.018
		a.f. 1.022	Alkaline	Negative	0.025
17	A. G.	b.f. 1.022	Acid	Negative	0.007
		d.f. 1.032	Alkaline	Negative	0.022
		a.f. 1.010	Acid	Negative	0.000
18	R. K.	b.f. 1.020	Acid	Negative	0.022
		d.f. 1.022	Acid	Negative	0.018
		a.f. 1.015	Acid	Negative	0.018
19	G. C.	b.f. 1.022	Acid	Negative	0.024
		d.f. 1.030	Acid	Negative	0.040
		a.f. 1.010	Acid	Negative	0.007
20	A. K.	b.f. 1.032	Acid	Negative	0.022
		d.f. 1.030	Alkaline	Negative	0.025
		a.f. 1.032	Alkaline	Negative	0.036
21	R. A.	b.f. 1.030	Acid	Negative	0.011
		d.f. 1.032	Acid	Negative	0.018
		a.f. 1.022	Acid	Negative	0.014
22	F. P.	b.f. 1.010	Acid	Negative	0.011
		d.f. 1.016	Acid	Negative	0.061
		a.f. 1.025	Acid	Cloud	0.086
23	C. D.	b.f. 1.030	Acid	Negative	0.007
		d.f. 1.025	Acid	Negative	0.011
		a.f. 1.040	Acid	Negative	0.022
24	W. C.	b.f. 1.012	Acid	Negative	0.004
		d.f. 1.022	Acid	Negative	0.022
		a.f. 1.016	Acid	Negative	0.011
25	E. S.	b.f. 1.018	Acid	Negative	0.007
		d.f. 1.018	Alkaline	Negative	0.032
		a.f. 1.015	Acid	Negative	0.025
26	R. S.	b.f. 1.025	Acid	Negative	0.025
		d.f. 1.032	Acid	Negative	0.007
		a.f. 1.022	Acid	Negative	0.001
27	E. F.	b.f. 1.020	Acid	Negative	0.011
		d.f. 1.020	Alkaline	Negative	0.007
		a.f. 1.020	Alkaline	Trace	0.022

TABLE 1.—URINE FINDINGS BEFORE, DURING AND AFTER FEVER.—(Continued.)

No.	Name.	Sp. gr.	Reaction.	Gross alb.	Quant. alb., per cent.
28	M. H.	b.f. 1.022 d.f. 1.025 a.f. 1.025	Alkaline Acid Acid	Negative Negative Trace	0.004 0.036 0.040
29	A. R.	b.f. 1.018 d.f. 1.024 a.f. 1.030	Acid Acid Acid	Negative Negative Negative	0.004 0.011 0.025
30	E. H.	b.f. 1.012 d.f. 1.025 a.f. 1.028	Acid Acid Acid	Negative Cloud Negative	0.007 0.374 0.032
31	M. H.	b.f. 1.025 d.f. 1.032 a.f. 1.010	Alkaline Alkaline Alkaline	Negative Trace Negative	0.014 0.043 0.018
32	E. W.	b.f. 1.010 d.f. 1.018 a.f. 1.018	Acid Acid Acid	Negative Negative Negative	0.004 0.007 0.007
33	R. L.	b.f. 1.020 d.f. 1.030 a.f. 1.025	Acid Alkaline Acid	Negative Negative Negative	0.007 0.005 0.011
34	A. B.	b.f. 1.025 d.f. 1.020 a.f. 1.030	Alkaline Alkaline Acid	Negative Negative Cloud	0.036 0.022 0.115
35	R. W.	b.f. 1.020 d.f. 1.030 a.f. 1.020	Alkaline Acid Acid	Negative Negative Negative	0.020 0.220 0.020
36	T. N.	b.f. 1.012 d.f. 1.018 a.f. 1.014	Acid Acid Acid	Negative Trace Negative	0.004 0.022 0.014
37	C. E.	b.f. 1.018 d.f. 1.020 a.f. 1.020	Acid Alkaline Acid	Negative Trace Negative	0.010 0.032 0.011
38	E. M.	b.f. 1.022 d.f. 1.020 a.f. 1.018	Alkaline Alkaline Alkaline	Negative Negative Negative	0.011 0.032 0.018
39	B. A.	b.f. 1.015 d.f. 1.010 a.f. 1.015	Alkaline Alkaline Acid	Negative Negative Negative	0.009 0.006 0.018
40	M. W.	b.f. 1.015 d.f. 1.020 a.f. 1.008	Acid Acid Acid	Negative Negative Negative	0.014 0.060 0.025

b.f. = before fever.

d.f. = during fever.

a.f. = after fever.

definite, being more than 100% in 20 of the subjects and over 200% in 16 cases. On 4 occasions the albumin level increased 500%. The complete tabulated results are:

Decrease.		Increase.	
No. of cases.	Per cent.	No. of cases.	Per cent.
2	0 to 50	4	0 to 50
7	50 to 100	7	51 to 100
—		4	101 to 200
9		5	201 to 300
		3	301 to 400
		4	401 to 500
		4	Over 500
		—	
		31	

This seems to prove conclusively that fever alone in the majority of cases provokes a rise in the amount of urine albumin. Frequently double or triple the normal level is reached.

It should be emphasized, however, that in spite of the rather large percentage rise, the actual albuminuria is not likely to be massive. During fever only 9 of the 40 cases showed albumin in the urine as determined by the sulphosalicylic acid method. One must remember, however, that the patients had a temperature

elevation for only a few hours. Had this been maintained for days, as is the rule in infectious fevers, it is probable that larger amounts would have appeared.

The relationship of the specific gravity to elevation of the temperature is shown in Table 1. While some increase in the specific gravity usually occurred during fever, this was never very great. Actually in 32.5% (13 subjects) the specific gravity remained at the pre-fever level or was decreased; in 8 of these there was a rise of the urine albumin. This fact indicates that the patients were not dehydrated (they ingested large amounts of normal saline solution during the treatment and did not lose weight). It follows, then, that *the increase in albumin was not relative* and due to dehydration with consequent increase in urinary concentration, but actually represented increased excretion due to fever.

Comparison of the pre-fever and post-fever urine albumin levels indicated that 70% of the subjects continued to show an increase in albumin in the specimens voided following return of the temperature to normal. This suggests that the increased output is carried over into the post-fever stage; the possible delay in voiding, however, must be considered in evaluating these results.

From those studied, the mechanism of the occurrence of albumin in the urine of febrile patients is not apparent. One can only say that it does occur and that it is not altogether a manifestation of existing toxemia and infection. A tenable explanation is that of cutaneous vasodilatation. This might produce a relative anoxemia of the kidneys with consequent increased membrane permeability. The possibility that the fever may have itself temporarily damaged the renal epithelium with temporarily increased permeability must also be considered.

Summary. 1. Forty patients have been studied from the standpoint of urinary albumin level before, during and after an uncomplicated fever.

2. True febrile albuminuria of varying degree occurs in over 75% of cases. This increased level is carried over into the post-fever stage.

3. The mechanism may be that of relative renal anoxemia following cutaneous vasodilatation.

BIBLIOGRAPHY.

- (1.) Bierman, W., and Fishberg, E. H.: J. Am. Med. Assn., 103, 1354, 1934.
- (2.) Cecil, R. L., and associates: Textbook of Medicine, W. B. Saunders Company, Philadelphia, 1931.
- (3.) Fishberg, A. M.: Hypertension and Nephritis, Lea & Febiger, Philadelphia, 1931.
- (4.) Gerhardt, C.: Ueber die Eiweisstoffe des Harnes, Deutsch. Arch. f. klin. Med., 5, 212, 1868.
- (5.) Hill, L. C.: Quart. J. Med., 22, 305, 1929.
- (6.) Kerridge, P. M. T., and Bayliss, L. E.: Lancet, 2, 785, 1932.
- (7.) Martin-Solon: Dell'Albuminurie, Béchét, Paris, 1838; cited by A. M. Fishberg.
- (8.) Osler, W., and McCrae, T.: The Principles and Practice of Medicine, D. Appleton & Co., New York, 1931.
- (9.) Shevky, M. G., and Stafford, D. D.: Arch. Int. Med., 32, 222, 1923.

HUMAN AUTONOMIC PHARMACOLOGY VI. GENERAL AND LOCAL SWEATING PRODUCED BY ACETYL-BETA-METHYLCHOLINE CHLORIDE (MECHOLYL).*

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ONE of the most prominent and spectacular responses of the autonomic nervous system to acetyl-beta-methylcholine chloride (mecholy) is the drenching perspiration.⁹ This effect of the drug occurs within a few minutes following a subcutaneous injection of sufficient dosage and is part of a general pouring out of secretions and excretions, including those from the mucous membranes of the eyes, nose, mouth, throat, and stomach. Generally speaking, from 15 to 30 mg. subcutaneously of mecholy will cause, in the average patient, a marked perspiration together with the systemic effects which have been described in the literature.

A general discussion of the sweating mechanism with references to a considerable part of the literature is given by Yas Kuno.⁵ He records the relationship between pilocarpine and atropine and discusses the theories of the sweat mechanism. Many early workers observed the alkalinity of the sweat, although references to this phenomenon seem to have disappeared from the literature. In 1852, Favre² observed that the sweat may pass over from acid to alkaline reaction. In the same year, a French writer, Gillibert d'Hercourt,³ noted the transition of the sweat from acidity to neutrality. In 1874, Robin¹¹ demonstrated this phenomenon. Heuss,⁴ studying the reaction to pilocarpine, definitely demonstrates this change of reaction. This is likewise noted by Camerer,¹ in 1902. Minor,⁷ in 1928, made possible the photography of sweat by his iodine paste technique.

The patients used in the following experiments were the same group we have used in our previously recorded experiments, namely, patients suffering from dementia præcox who are otherwise healthy and who present no marked vasomotor disturbance. Whatever

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control experiments we have done on normal individuals show that these patients, so far as sweating reactions are concerned, may be considered normal.

We record here certain phenomena not hitherto described in the literature which are of importance in respect to the physiology of the sweat mechanism.

1. *The Alkalinity of the Mecholyl Sweating Reaction.* It is currently and commonly stated in the literature that sweat is acid. This is true if the usual technique is followed; that is, if a piece of litmus paper is rubbed over a sweating zone and rubbed against the skin. In 1878, Trümper and Luchsinger¹² noted that sweat produced by pilocarpine was alkaline. Furthermore, these authors noted that the production of sweat under pilocarpine on a previously washed side of the face was immediately alkaline as compared with the sweat on the unwashed side of the face which was acid, and which later also became alkaline. Metzner,⁶ carrying the observations of these authors further, explained that the acid reaction of sweat was due to fatty acids normally present in the skin, and that if these were removed, sweat usually was somewhat alkaline.

The sweat produced by mecholyl is always alkaline if care is taken to test the sweat droplet and not rub the litmus paper against the skin. Furthermore, if the skin is previously thoroughly cleansed by soap, water, alcohol, and ether, the sweat is universally alkaline following any technique used; that is, immediately following the mecholyl injection the sweat becomes definitely and decidedly alkaline.

pH determinations made in two subjects showed that following subcutaneous injection of 25 mg. of mecholyl, the pH changed from 6.1 to 8.1 in 1 case, and from 7.5 to 8.5 in the other. This increase in alkalinity is in harmony with results which we record elsewhere;⁸ namely, that mecholyl changes the acid secretion of the stomach to alkaline, and is in line with observations made more roughly which indicate that the tears, nasal secretion and saliva are rendered more alkaline by this chemical. In other words, the increased alkalinity of the sweat is part of a general reaction of the excretions and secretions of the body.

2. *Effect of Atropine on the Mecholyl Sweat.* Atropine, given in advance of the mecholyl injection in dosage from 1/100 to 1/50 gr. prevents the sweating reaction, just as it prevents all other mecholyl responses. Atropine, given at the height of the sweating reaction, stops the sweating within a few moments of the injection.

3. *The Synergic Effect of Prostigmin.* It has been shown by many workers that physostigmin and prostigmin are synergic in relationship to the effects of mecholyl and acetylcholine derivatives in general.¹⁰ We have shown this to be true in the case of the gastric secretions in man; that is, a small dose of mecholyl will produce no changes of substantial nature in the gastric secretion, but if a preliminary

treatment with prostigmin or physostigmin is given, the same dose of meeholyl will produce marked changes in gastric secretion.

This is also true of the sweat reaction: 10 mg. of meeholyl injected subcutaneously will, in the average patient weighing about 125 to 150 pounds, produce slight, if any, sweating. If, preceding this injection, the same patient receives 1 cc. of 1 to 2000 prostigmin or $\frac{1}{8}$ gr. of physostigmin, the sweating reaction becomes marked and definitely alkaline.

4. *The Intradermal Sweat Reaction of Meeholyl.* A. It was observed by us that following a subcutaneous injection of meeholyl for the purposes of producing the general reaction, there was more sweating around the site of the injection than elsewhere. We consequently carried out a series of experiments on the effect of intradermal injections of dilute solutions of meeholyl. An intradermal injection of 0.1 to 0.2 cc. of 1 to 1000 meeholyl solution will, in the great majority of individuals tested, produce a wheal, then a gradual flushing on the periphery of the wheal, which gradually includes the wheal.* This is followed by a slow elevation of the sweat glandules and then glistening drops of sweat appear at the apex of each gland. Finally, the whole wheal becomes covered with either a thin layer of sweat or is profusely drenched, according to the sensitivity of the individual and the general environmental conditions, such as the heat of the day. This sweat is immediately alkaline, and especially so if the droplets are carefully tested without contact with the skin, and quite universally so if the skin has previously been treated as indicated in the preceding part of this paper.

This local sweating, as we have named it, is very variable in the dosage required to bring it about. In one of our subjects, a member of the research staff, 0.2 cc. of a 1 to 1,000,000 solution was sufficient to effect it. We are of the impression that the sweating reaction decreases in old age, although this has not been studied sufficiently to be established.

B. Control studies with salt solution, adrenalin, benzedrine and distilled water produced no local sweating reaction.

C. The effect of a general sensitization by prostigmin or physostigmin. When 1 cc. of 1 to 2000 prostigmin was given by subcutaneous injection, the sweating observed became increased, and in cases where the dilution of meeholyl was so great as to be without any result in sweating, sweat appeared following the prostigmin injection.

D. If 0.1 cc. of 1 to 2000 prostigmin is mixed with 1 to 1000 meeholyl in equal parts and the combination injected intradermally,

* The seasonal relationship of sweating comes out very importantly in our later experiments. The general sweating reaction is not nearly so profuse in the fall as it is in the summer. The intradermal sweating test at the time of this writing (November) requires a concentration of 1:200 to bring about a good sweating response in those patients in whom 1:1000 was sufficient 3 months ago.

the result in sweating is always greater than when 0.2 cc. of 1 to 1000 mecholyl is given intradermally at the same time and on the opposite side of the chest wall.

E. A very dilute solution of atropine injected into one side of the wheal stops the local sweating.

F. Adrenalin injected into one side of the mecholyl wheal stops the sweating wherever it produces a marked vasoconstriction. Where there is no vasoconstriction, the mecholyl sweating proceeds as before. Benzedrine, on the other hand, given intradermally has no effect upon the local sweating.

5. *The Effect of Iontophoresis on the Sweat Reaction.* Iontophoresis was carried on in the usual way; that is, the negative electrode was moistened with salt solution, and the positive electrode moistened with 1 to 1000 mecholyl solution. After the application of 4 milliampères of current for a period of 5 minutes, the electrodes were removed and the skin reaction watched. Within a few minutes the same reaction appeared as followed the intradermal reaction; namely, flushing, elevation of the sweat glands, and the appearance of glistening drops of sweat, which sweat was alkaline. In other words, the galvanic current had introduced the mecholyl into the skin and an intradermal reaction was produced, differing in no way from the direct intradermal injection.

Summary. 1. The human organism is very sensitive to acetyl-beta-methylcholine chloride (mecholyl) and especially the sweat mechanism.

2. Sweat produced by mecholyl is alkaline, and the alkalinity increases as the reaction goes on.

3. The general sweating reaction can be inhibited by atropine as completely as all the other cholinergic effects of mecholyl.

4. On the other hand, the sweating is enhanced by the drugs synergic to mecholyl, that is, *prostigmin* and *physostigmin*.

5. An interesting intradermal local sweating response is here described. This intradermal response is abolished by atropine, and in small doses atropine acts on the local mechanism to prevent the appearance of sweating. Adrenalin inhibits this local intradermal response only by virtue of its vasoconstriction action, since the reaction persists where vasoconstriction does not appear. Sodium chloride and benzedrine were observed to have no effect on the local sweating response.

6. The local sweating response differs in various individuals and may be a criterion of the sensitivity of the individual to parasympathetic or cholinergic stimulation.

REFERENCES.

- (1.) Camerer, W.: *Ztschr. f. Biol.*, 41, 271, 1902. (2.) Favre, P. A.: *Compt. rend. Soc. de biol.*, p. 721, 1852. (3.) d'Hercourt, G.: *Gazette medicale de Lyon*, 1852; cited by Trümpy, D., and Luchsinger, B., in *Pflüger's Arch.*, 18, 495, 1875. (4.) Heuss, E.: *Monatschr. f. prakt. Dermat.*, 14 Bd., Nos. 9, 10, 12, *Malys Jahresber.*

f. Tierchemie 22, p. 193. (5.) Kuno, Yas: The Physiology of Human Perspiration, London, I. and A. Churchill, Ltd., 1934. (6.) Metzner, R.: Nagel's Handbuch der Physiologie des Menschen, Vieweg, Braunschweig, 1907. (7.) Minor, V.: Deutsch. z. f. Nervenheilk., 101, 302, 1928. (8.) Myerson, A., Dameshek, W., and Rinkel, M.: New England J. Med. 215, 1005, 1936. (9.) Myerson, A., Loman, J., and Dameshek, W.: AM. J. MED. SCI., 193, 198, 1937. (10.) Myerson, A., Loman, J., and Rinkel, M.: (In press). (11.) Robin, A.: J. de therap., vol. 23, p. 881; vol. 24, p. 930; cited in Virchow's Jahresbericht, IX, Jahrg. Band I, p. 509, 1874. (12.) Trümper, D., and Luchsinger, B.: Pflüger's Arch., 18, 494, 1878.

OTHER REFERENCES CONSULTED.

Bogdan, S.: J. de physiol. et de path. génér., 6, 1009, 1904. Brücke, F. T.: Klin. Wehnschr., 14, 7, 1935. Dale, H. H., and Feldberg, W.: J. Physiol., 82, 121, 1934. Grigoresco, D., and Jordanesco, C.: Vol. jubilaire, Marinesco, p. 249, 1933, Bucarest, Société Roumaine de Neurologie, Psychiatrie et Endocrinologie. Koppányi, T., Dille, J. M., and Linegar, C. R.: J. Pharm. and Exp. Therap., 58, 105, 1936. Ottenstein, B., and Böhm, A.: Klin. Wehnschr., 14, 275, 1935.

THE CLINICAL EFFECTIVENESS OF LACTIC ACID JELLY AS A CONTRACEPTIVE.

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IN spite of its great importance to both this generation and the next, contraception in its medical and physiologic aspects has been given relatively little attention by scientific investigators. This has been due in part to the "taboo" which, to a steadily diminishing degree, custom has imposed on the discussion of matters relating to sex; in part, to the unfounded classification of contraceptives with "obscene matter" in various laws; and, in part, to the conservatism of the boards of trustees under whom research work is carried on. An outstanding example of this conservatism is furnished by the American Medical Association, which, in spite of the medical character of contraceptives and of their widespread use by its members, does not yet permit its Council on Pharmacy and Chemistry to report on their ingredients or on their safety or effectiveness. For these reasons a careful evaluation of contraceptives would appear worth while.

The experience of the birth control clinics has demonstrated the necessity for research into simpler and more generally acceptable methods of contraception than those now used by the clinics. It has become evident that high percentages of success with the diaphragm and jelly method have been achieved by patients using the method carefully. At the same time it has been found that only about half of the patients of many birth control clinics are willing to follow the method with care.

Conscious of an obligation to their patients, the physicians of

birth control clinics have been unwilling to experiment widely with alternative techniques in the hope of finding more acceptable methods of adequate reliability. Exploiting commercial interests, however, have not hesitated to develop a market for some of the materials which appear to be simpler in use and perhaps less expensive than the jelly and diaphragm combination. Of these, jelly used alone especially warrants a careful statistical study at the present time.

Dr. Irving Stein (personal communication) distributed tubes of jelly, each provided with a nozzle, to underprivileged patients. The proper procedure was carefully explained in each case by a social worker who also made repeated visits to the home in order to encourage persistence in the method. Interruption of supplies of jelly made continuous records difficult. Calculating from the time the supplies were first given to the date of the last follow-up in each case, Dr. Stein finds that 112 patients had 44 person-years of exposure to the risk of pregnancy with no pregnancies. Six other patients also had no pregnancies, but the duration of the periods of their exposure is not known. Dr. Stein states that pregnancies occurred after it became necessary to discontinue the social worker. These may have been due in part to the lack of her periodic encouragement.

The jelly used in that experiment was prepared from the following formula:

	Weight %.
Boric acid	2.58
Lactic acid	2.00
Glycerine	9.57
Powdered tragacanth	2.39
Water	83.46

Recent samples have been found to have a pH of about 2.

More recently, Mr. A. R. Kaufman, of Kitchener, Ontario, Canada (personal communication) has distributed contraceptive jelly to over 35,000 cases. A follow-up was made of 1000 of these by comparing the names of the recipients with those in the official birth records of 3 cities. It was found that after 18 months children had been born to 20% of those receiving supplies. It is impossible to convert these figures into pregnancies per hundred years of use of jelly since approximately one-third of the original thousand received condoms with the jelly and nozzle. The pregnancy rate for the combination would appear to lie between 13 and 26 per 1000 person-years of use. That only a small number of these pregnancies occurred while the method was being properly employed is suggested by the reasons given by the users for the failures. These were:

Reason.	Per cent of failures.
Failure to renew supplies	41
Irregular use	47
Condom broke	3
Failure of jelly	9

The jelly employed was said to consist of 1% of lactic acid and 4% of boric acid in a base of glycerite of starch. In the process of manufacture the boric acid was converted into boroglyceride.

Another brief series is available as a result of work done in a mountain community in West Virginia. Jelly was distributed in jars and each patient was given a bulb and syringe applicator which delivered into the vagina a dose of approximately 6 cc. Forty-three cases show a total exposure to pregnancy of 308 months, or roughly 26 years, with 11 undesired pregnancies, or 43 pregnancies per 100 person-years of exposure to the risk of pregnancy. Of these 11 pregnancies, 7 resulted from failure to follow directions carefully. When allowance is made for this fact, 36 patients are found to have had an exposure of 19 years with 4 pregnancies, or 21 pregnancies per 100 person-years of exposure. The qualitative formula as given by the manufacturer is as follows: lactic acid, quinine bi-sulphate, zinc sulpho-carbolate, oxyquinoline sulphate, resorcinol, glycerine, and gum tragacanth. The examination of one sample revealed a pH of 2.9.

In the obstetrical department of the Episcopal Hospital in Philadelphia, located in a manufacturing district, tubes of jelly provided with nozzles were offered to each post-natal case approximately 1 month after delivery. Each patient was informed that the method did not give perfect protection and that she would be given the address of a diaphragm clinic in the neighborhood should she prefer. A charge of \$0.20 was made for each tube of jelly and \$0.10 for each nozzle. To those purchasing jelly, careful instructions were given for its use. The patients were advised that additional security would result from the simultaneous use of a condom and by avoidance of the more fertile period of the menstrual cycle.

The jelly used was said by the manufacturer to contain 2% lactic acid and 0.025% oxyquinoline sulphate in a vegetable gum base. Recently secured samples were found to have a pH of 2.9.

An attempt was made 26 months after the series was begun, to follow up all the cases more than 6 months old. Of 130 cases it was possible to locate and interview only 83. It is apparent that the selection of cases was not random, but on the basis of proven fertility and sufficient interest in contraception to purchase a tube of jelly and a nozzle for 30 cents.

The 83 patients divided into 3 groups: Group I, those who were regular and careful users; Group II, those who used the jelly irregularly or who discontinued its use; and Group III, those who never used the jelly. Table 1 presents the data essential for a calculation of the pregnancy rates of these three groups during the period in which the jelly was supposed to have been used, together with the same information for those 12 women who became pregnant during this period.

TABLE 1.—PREGNANCY RATES AMONG USERS AND NON-USERS OF JELLY.

Extent of use. (1)	No. of cases. (2)	Per cent of all cases. (3)	Exposure to pregnancy in years.		No. of pregnancies.		Pregnancies per 100 person-years exposure to risk of pregnancy.	
			Undesired. (4)	All. (5)	Undesired. (6)	All. (7)	Undesired. (8)	All. (9)
Group I . . .	19*	23	26	26	1	1	4	4
Group II . . .	42	56	56	57	5	6	9	11
Group III . . .	22	26	22	23	4	6	18	26
Total . . .	83	100	104	106	10	13	10	12
Those who became pregnant	12	14	9.1	10.7	10	13	110	121

It seems probable that the pregnancy rates of Table 1 are somewhat lowered by the fact that all the cases here reported are post-natal, and that no allowances have been made for this characteristic. The interval between parturition and purchase of the jelly is similar for all groups, however, so that this factor cannot account for the observed differences in the pregnancy rates.

What is essential, of course, in the evaluation of the effectiveness of any contraceptive method is an estimate of the number of pregnancies which would have occurred had not the particular contraceptive method been used. No highly accurate estimate can be made here, but it is useful to compare the pregnancy rates for all pregnancies in the period of using the jelly with the rates for all pregnancies before the jelly was purchased (Table 2).

TABLE 2.—COMPARISON OF PREGNANCY RATES BEFORE AND AFTER PURCHASE OF THE JELLY.

Extent of use (1)	Exposure before purchase in years. (2)	No. of pregnancies before purchase. (3)	Pregnancies per 100 person-years exposure to risk of pregnancy.		
			Before purchase. (4)	After purchase.	
				Undesired. (5)	All (6)
I	72	57	79	4	4
II	162	114	70	9	11
III	89	53	60	18	26
Total	323	224	69	10	12
Those who became pregnant . . .	27	31	115	110	121

The method for calculating pregnancy rates has been adapted from Pearl¹ and from Stix and Notestein.² From the gross period of exposure the following deductions have been made for infertility:

10 months for each full term pregnancy terminating in live issue; 9 months for each stillbirth; 3 months for each abortion or miscarriage. Those who became pregnant after purchasing the jelly are shown to have had a previous fertility considerably higher than that of the entire series. The differences in fertility before purchasing the jelly are not significant for Groups I, II, and III. Hence the differences among Groups I, II, and III in respect to pregnancy rates while using the jelly cannot be explained in terms of previously demonstrated fertility.

No significant differences were found among the three groups as to educational attainment, age at the time of purchasing the jelly, number of pregnancies at the time of purchasing the jelly, length of marriage at this time, interval between parturition and purchase of jelly, or length of exposure to pregnancy after purchase of jelly. As 43, or more than 50% of all the cases, used on an unspecified number of occasions some method of contraception other than jelly alone, the latter cannot be considered entirely responsible for the reductions in fertility. The extent to which the use of methods alternative or supplementary to jelly alone depressed the observed rates cannot be determined in this preliminary report. The effect of supplementary methods is obvious in Group III, in which 3 were separated from their husbands or employed abstinence, 8 used the condom, and 1 resorted to coitus interruptus. The 9 contraceptive users had a total exposure of 13.4 years with no pregnancies. The 10 remaining in Group III, and stating they had used no contraceptive method, had a net exposure of 9.8 years with 6 pregnancies, making a pregnancy rate of 61 per 100 person-years of exposure to the risk of pregnancy. Although they may account for part of the difference between the rates for Groups II and III, however, differences in the degree of resort to alternative or supplementary methods do not explain the observed differences in the pregnancy rates of Groups I and II. In Group I only 4 admitted the use of methods supplementary to the jelly; 3 employed the condom and 1 the condom and douche, to an unknown extent, without ceasing the regular use of the jelly. In Group II, 30 admitted the occasional use of alternative, supplementary, or substitute methods; 13 relied on the condom, 10 on the condom and douche, 6 on the douche, and 1 on a different jelly. No case in any group stated that the "safe period" method had been used.

Average frequency of coitus was examined and certain differences obtained. For Group I the mean frequency per week was 1.41; for Group II it was 1.73; for Group III it was 1.79; and for those 12 who became pregnant the mean was 1.93. These differences, however, do not appear to be large enough to account for the differences in pregnancy rates.

In following up these 83 cases, care was taken to obtain the

alleged reasons for not using the jelly regularly and carefully. Table 3 presents the frequencies with which the various reasons were given.

TABLE 3.—REASONS GIVEN FOR NOT USING JELLY REGULARLY AND CAREFULLY.

Reason.	Number.	Per cent.
1. Carelessness or negligence	17	26
2. Lack of confidence*	13	20
3. Difficulties in obtaining	7	11
4. Esthetic objections	7	10
5. No reason	5	8
6. Preferred another method	5	7
7. Health objections	3	5
8. Pregnancy desired	3	5
9. No coitus	3	4
10. Religion	2	3
11. Menstruation not resumed	1	2
Total	66	101

* The number of cases in this group was probably increased by the physician's recommendation of the condom and the "safe period" as methods supplementary to the use of the jelly.

Conclusions. 1. An acid contraceptive jelly used both alone and with occasional supplements, gave reasonable protection against undesired pregnancy..

2. A group of 19 patients who used jelly regularly, 4 of whom admitted the use of supplementary methods, and whose total exposure was 26 years, had undesired pregnancies at the rate of 4 per 100 person-years of exposure to the risk of pregnancy.

3. Of 42 others using the method intermittently, 30 relied in part on other methods. The total exposure was 56 years, and the rate for undesired pregnancies was 9 per 100 person-years.

4. A comparable group of 22 patients in the series did not use the jelly they purchased but half of them employed other contraceptive methods, reducing the rate for undesired pregnancies to 18 per 100 person-years of exposure.

5. The average pregnancy rate for all pregnancies in the entire series of 83 patients before the purchase of the jelly was 69 per 100 person-years of exposure.

6. Of 83 patients who purchased contraceptive jelly 1 month after delivery, 23% used the jelly faithfully, 51% intermittently, and 26% never used it. The acceptability of the jelly, modified by the conditions of its prescription, appears low.

Since this article went to press, Dr. Hannah Stone³ has reported an excellent clinical study of contraceptive jellies. The data given do not permit a direct comparison of the results with those here reported.

REFERENCES.

- (1.) Pearl, R.: Human Biology, 4, 400-401, 1932. (2.) Stir, R. K., and Notestein, F. W.: Milbank Mem. Fund Quart., 13, 167-169, 1935. (3.) Stone, H. M.: J. of Contraception, 1, 209, 1936.

DIABETES AND PREGNANCY.

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SINCE the introduction of insulin, an increasing number of diabetics have become pregnant due to prolongation of the lives of juvenile diabetics and the increased fertility of adult diabetics. In the future, we must expect the occurrence of pregnancy in diabetes to engage with increasing frequency the attention of both the internist and the obstetrician. This paper deals with maternal mortality in diabetics, the fetal death rate, diagnosis, and the medical and obstetrical care of such women.

Maternal Mortality. In 118 cases collected by Skipper⁸ there was a maternal mortality rate of 9.3%, although none of his own 33 cases died. Williams¹¹ found, in 1909, a death rate of 27%. In the 51 diabetics delivered at the Boston Lying-in Hospital since 1916 there were no deaths from diabetes, the sole fatality being in a woman who had severe eclampsia. We may assume, therefore, that the outlook is good for a diabetic woman contemplating pregnancy.

Fetal Mortality. Skipper found a gross fetal mortality of 45.2% in his collected cases, which is no improvement over the 41% reported by Williams before the days of insulin. In Skipper's own 33 hospital cases there was a fetal death rate of 40%. In his last 13 cases, treated with special care, 3 babies died, a mortality of 23%.

At this hospital between 1916 and 1932 there were 34 diabetic pregnancies which were productive of 35 infants, since there was one pair of twins. Of these, 15 were non-viable, stillborn, or died after birth, giving a gross fetal mortality of 42.8%. Of more importance from the standpoint of the hospital is the death rate among infants that had a fair prospect of survival when their mothers first presented themselves at the clinic. If the fetus is alive *in utero* when the patient first applies for treatment, if it is not malformed or under 4 pounds when delivered, we believe that such an infant should have a good prognosis for life. A stillbirth or neonatal death occurring in this group is a net fetal mortality. Of the 35 infants, 28 belonged in this category, and 7 of them died, a net mortality of only 25%.

Since 1932, the care of all diabetics has been under the supervision of the authors of this report. There have been 18 diabetic pregnancies. One of the patients was first seen in coma with a dead

fetus undelivered. Two other infants were stillborn or died after birth, giving a gross fetal mortality of 16.7%. There were 17 cases in which a living infant might have been expected, with two deaths, a net fetal mortality of 11.7%. It is therefore apparent, so far as one may draw conclusions from a small number of cases, that both the gross and the net fetal mortality have been decreased by half. The two stillbirths occurred in Cases 3 and 12. In Case 3 the baby died early in the last month. Unfortunately, a postmortem examination could not be obtained. In Case 12 the baby died $4\frac{1}{2}$ weeks before term. This baby, while it appeared normal externally, showed a large heart with glycogen infiltration of the myocardium at postmortem. A Cesarean done 2 weeks from term could not have saved either baby.

It would seem that there are three factors involved in the high fetal mortality of diabetes. These are: 1, neglect of the disease, either by the patient or by the physician, resulting in acidosis; 2, excessive size of the fetus; and 3, an increased frequency of fetal anomalies. From our own experience, as well as from a study of the literature, the most frequent cause of fetal death is neglect of the diabetes with resultant acidosis. Four of our 18 infants weighed 10 pounds or more; and the average weight was 8 pounds, 11 ounces, so that these babies appear to be larger than normal. Three per cent of the infants in Skipper's collected cases had congenital abnormalities. Three of the 53 infants in this hospital's cases (5.7%) presented malformations inconsistent with life. Of less importance are fetal hyperglycemia and congenital diabetes. Hydrannios is less frequent since the introduction of insulin.

Diagnosis. Lactosuria may occur in the latter months of pregnancy and be confused with diabetes. Non-diabetic glycosuria is more frequent in the pregnant than in the non-pregnant. It is usually ascribed to lowering of the renal threshold, but there is also a slightly impaired carbohydrate utilization, producing a high initial alimentary hyperglycemia, as is demonstrated by the following example:

<i>Before delivery.</i>			<i>After delivery.</i>		
Hours.	Blood sugar.	Urine.	Hours.	Blood sugar.	Urine.
0 . . .	102	..	0 . . .	88	Green
$\frac{1}{2}$. . .	178	0	$\frac{1}{2}$. . .	146	Green
$1\frac{1}{2}$. . .	202	Yellow brown	$1\frac{1}{2}$. . .	138	Green
3 . . .	91	Yellow brown	3 . . .	90	Green

The fermentation test distinguishes glucose from lactose. In all cases where sugar is found in the urine we perform blood sugar tests 2 hours after meals or glucose tolerance tests. With lactosuria there should be no marked elevation of the blood sugar. We have made the diagnosis of diabetes only if the fasting blood sugar is 120 mg. % or more, or if the blood sugar 3 hours after the ingestion of 100 gm. of glucose is 120 mg. % or more. Several patients presented high

intermediate curves, but since the blood sugar was not elevated at the end of 3 hours we did not consider them diabetics, although they were carefully observed subsequently. None of them experienced any difficulty at delivery or in the puerperium, nor did they develop positive evidence of diabetes. One of our patients (Case 10) was first seen when 7 months pregnant with the following sugar tolerance tests.

<i>Before delivery.</i>			<i>7 weeks after delivery.</i>		
Hours.	Blood sugar.	Urine.	Hours.	Blood sugar.	Urine.
0	143	Brown	0	116	0
$\frac{1}{2}$	222	Red	$\frac{1}{2}$	167	Trace
2	153	Brown	2	83	Trace
3	125	Yellow			
A diabetic curve.			A non-diabetic curve.		

Another curve determined a year postpartum was also non-diabetic, indicating that the patient had suffered from mild diabetes according to our standards, which improved after pregnancy. Two other patients (Cases 17 and 18) behaved in a similar fashion. They were both fat women. There was also one patient with known renal glycosuria. There is still a great deal to be learned about carbohydrate metabolism in normal pregnancy. It is possible that our standards are too low although they are the most stringent in the literature.

Management of Diabetes During Pregnancy. Once the diagnosis is made the patient is usually admitted to the hospital a few days for regulation and instruction. She is given a diet of 150 gm. of carbohydrate, 70 to 80 gm. of protein and fat according to the state of her nutrition. One quart of milk a day is included and she is given cod-liver oil or viosterol. Pre-meal specimens of the urine are examined. If the glycosuria continues, insulin is administered until it is controlled. On several occasions we were surprised to find that the patient needed more insulin than we had expected from the degree of glycosuria. If the gravida is in the last month of pregnancy, stereoroentgenometric measurements of the fetus are made according to the method of Johnson.⁴ She is sent home with instructions to test her urine before each meal and at bedtime until we are sure that there is no sudden shift in tolerance. She is then seen at weekly intervals.

It is generally believed that there is a definite improvement in diabetes during pregnancy because of the increased insulin supply produced by the fetal pancreas. This view is supported by the work of Carlson and Drennan,¹ and of Carlson and Ginsburg,² who found that the diabetes produced by pancreatectomy in pregnant bitches was far less severe than that in the non-pregnant. This work was repeated by Markowitz and Soskin⁵ who found, on the contrary, that pancreatectomy in pregnant dogs resulted in diabetes of the same severity as that in the normal controls. Further, they found

SUMMARY OF FINDINGS IN AUTHORS' CASES OF DIABETES AND PREGNANCY, 1932-1936.

Name.	Para. Age.	Family history of diabetes.	Obstetrical history.	Onset of diabetes.	Insulin before pregnancy.	Insulin during pregnancy.					Insulin after delivery.	Method of delivery.	Condition of baby.*	Lactation.	Complications.	Remarks.
						0-4 m.	5 m.	6 m.	7 m.	8 m.	9 m.					
1. C. W. due Jan. '33	i	Grandfather	10 yrs. ago	40	40	70	70-75	70-75	70-75	70-75	Normal	7 lbs. 13 oz.	Poor	Toxemia, pyelitis postpartum	
2. F. A. due Aug. '33	ii	0	1931-39 lb. living child	6th mo. of this preg.	52	60	64	Normal labor induced by castor oil and rupture of membranes	8 lbs. 7 1/2 oz.	Poor		
3. M. K. due Sept. '33	v	0	3 91 lb. living children 1929-died at 10 d. (last preg.) of atresia of bowel	4 yrs. ago during last preg.	...	0	0	0	0	0	0	Normal	10 lbs. stillborn	...	Bell's palsy	
4. E. O. due Sept. '33	iv	1 sister	1924-7 lbs., lived 12 hrs. 1925-11 1/2 lbs., stillb. 1926-Cesarean for toxemia, live child, 6 lbs.	3 yrs. ago (5 yrs. after last preg.)	Had rec. as much as 55 units at beg. of preg. 8-10	8, 16, 24	28	..	32	14	0	Cesarean, and sterilization	7 lbs. 13 oz.	Poor	Toxemia, severe	
5. L. J. due Dec. '33	i	Father Brother Sister	Found at beg. of this preg.	15	60	60	0	Normal	7 lbs. 14 oz.	Poor	Admitted 10 days before due; needed no insulin
6. I. M. due Nov. '33	vi	Mother and sister died diabetes	1917-premature 4 1/2 lbs., 1918-10 1/2 lbs., L. and W. 1920-12 1/2 lbs., L. and W. 1920-13 1/2 lbs., stillb. 1928-12 1/2 lbs., L. and W.	7th mo. of this preg.	20	20	20	Normal	7 lbs. 15 oz. congenital ht. disease	Poor	Bell's palsy	Entered with ac-dosis (bronchopneumonia)
7. D. A. due June '34	i	0	3 yrs. bef. preg.	48	45	40	60	60	60	60	Normal	7 lbs. 14 oz.	Good, then scanty	Pyelitis postpartum	Required 60 units postpartum, until pyelitis subsided
8. M. G. due Aug. '34	iv	Brother	1920-5 mos. stillb. 1928-15 lbs. stillb. 1931-diabetic preg. Poor treatment, stillb.	3 yrs. ago	32	32	32	32	85	75	75	Cesarean, spinal	10 lbs. Two weeks from term	Poor	Entered showing +++++ acetone; under 7 months. preg. when seen
9. M. N. due Feb. 5, '34	iv	..	1927-normal, L. and W. 1930-8 mos., stillb. 1932-7 mos., stillb. poor management	12 yrs. ago	10	10-20 units	10-20 units	10-20 units	10-20 units	10-20 units	70-22 units	Normal	5 lbs. 9 oz. stillborn	..	Entered in coma. fetal movements present until 1-2 hrs. before entry	On admission, no fetal heart heard. Not seen before admission in coma

10 V. S. due July '31	ii	27	0	1929—2 mos. abortion 1930—misc. 1931—toxemia, live baby, 7 lbs. 1 oz.	...	0	0	0	0	0	0	0	0	Normal breech extraction	7 lbs. 10½ oz.	Good	Brown test for sugar found when 7 mos. preg.	SUGAR TOLERANCE During After preg. del. 0 113 116 1 222 167 2 153 83 3 125
11. I. V. due Feb. '35	iv	35	0	1930—0½ lbs., stillb. 1932—13 lb., stillb. 1933—? died at birth	Discovered after deliv.	0	0	0	0	0	0	0	0	170-0 Cesarean	11 lbs. 3 oz. ? mental re- tardation	0	B. coli septicemia	Transferred to Beth Israel Hosp. Got well
12. M. M. due July '35	i	30	0	During 6th mos. of preg.	50	50	50	50	10	Normal	8 lbs. 10 oz. Macerated P.M. showed large lft. with glycogen in- filtration	0	Hydramnios	Patient preg. again now†
13 D. R. due Aug. '35	iv	39	0	1918—7½ lb., L. and W. 1920—3 mos., miscar. 1921—10 lb., L. and W. 1926—miscarr. 1931—7½ lb., died later, congen. heart 1931—10 lb., died at 1 day of intracran. hem.	2 yrs. ago	0	0	0	0	32	40	50	0	Normal	10 lbs. 11 oz.	+	0	Baby had erythro- blastosis with re- covery
14. D. M. due Nov. '35	vii	31	0	1921—0½ lb., L. and W. 1925—5 lb., L. and W. 1927—6½ lbs., L. and W. 1933—miscarr. 1930—6 lbs., L. and W. 1932—3½ lbs., L. and W.	Prob. dur- ing last preg.	15	15	18	18	30	30	36	16-0	Normal	7 lbs., 11 oz.	++	0	
15. S. L. due Aug. '35	ii	38	Mother	1933—6½ lbs., died of cry- throblastosis	During 7th mo. of this preg.					10	20	0	0	Normal	8 lbs.	0	0	
16 B. S. due Sept. '35	iii	36	0	1920—7 lbs. 1922—7½ lbs.	During 6th mo. of this preg.				0	0	0	0	0	Normal	7 lbs. 6 oz.	0	0	
17. B. D. due Feb. '36	iv	38	0	1920—9 lb. baby crippled at birth 1925—12½ lbs., L. and W. 1929—6 lbs., L. and W.	During 8th mo.									Normal	10 lbs 11½ oz.	++	0	SUGAR TOLERANCE During After preg. del. 0 102 102 1 277 236 2 222 204 3 123 80
18. M. T. due Apr. '36	ix	10	0	1916—7½ lbs., prem. 1918—6½ lbs., L. and W. 1923—stillb. twins, 7 lbs each 1924—15 lbs., died at 11 yrs 1925—10 lbs., died at 11 mos. 1927—10.4, L. and W. 1930—7 lbs., L. and W. 1931—0½ lbs., L. and W.	During 8th mo.	...								Normal	10 lbs. 12 oz.	++	0	SUGAR TOLERANCE During After preg. del. 0 161 92 1 256 133 2 286 123 3 159 82

* All babies alive and well unless otherwise stated.

† Patient delivered normally on July, 1936, of 9 lb., 2 oz. baby.

that pregnancy in pancreatectomized dogs was not accompanied by a decrease in insulin requirement.

The findings in our 18 cases are shown in Table 1. Six of these patients had a family history of diabetes, and of the 6, 3 had diabetes before they became pregnant. Twelve cases required 20 or more units of insulin a day and 1 needed as much as 85 units a day, thus classified as moderately severe. Four were sufficiently mild to be diagnosed definitely only after a sugar tolerance test. With the exception of those cases that never needed insulin, the insulin requirement of all patients increased during pregnancy. Case 4, however, needed less insulin as gestation advanced, probably because she was more coöperative than before her pregnancy. The rise in insulin requirement was often sudden. This shift occurred in the middle trimester, usually at about 5 months. Cases under competent management would suddenly show increased glycosuria and acetonuria. For this reason, it was necessary to admit Cases 7 and 8 to the hospital. In a few instances, insulin reactions occurred just before term and the dose was therefore reduced slightly. After taking 60 units a day during pregnancy Case 5 became sugar free without insulin 10 days before term. This case illustrates the necessity for weekly observations to make adjustments in insulin requirement.

All of our patients needed less insulin in the puerperium. *In no case was the diabetes more severe than before delivery.* We may assure the diabetic woman not only that pregnancy will not increase the risk to her life, but also that it will not make her diabetes worse.

Management of the Diabetes During Labor. The diabetic should be seen by both the internist and obstetrician as soon as she starts in labor and constantly until after she is delivered and out of danger. She should be kept free of acetone. Since ketosis is easily developed in the normal pregnant patient it is even more readily produced in the diabetic. During labor the urine is tested every 2 hours and insulin given according to the amount of sugar found. In the early first stage, when the patient is able to drink, fruit juices and insulin are given. If acetonuria is present 500 cc. of 15% glucose is administered intravenously unless we are sure the patient can take fluids and carbohydrates by mouth. In all cases, except the very mild ones, before leaving the delivery bed, the patient is given normal saline by hypodermoclysis and from 300 to 500 cc. of 15 to 20% glucose intravenously.

Method of Delivery. All diabetics, of whatever severity, unless they present obstetrical abnormalities, are delivered through the pelvis, and normally if possible. Toward the diabetic who has a large fetus we allow a greater latitude. Upon her we perform a Cesarean section a week or 10 days before term. The indication in such a situation is one of relative dystocia, and has no bearing on her medical condition. In the early group of 34 diabetics at this

hospital, Cesarean section was performed 5 times; in the later group of 18 cases, under present discussion, it was performed 3 times, an incidence for the combined series of once in every 8.75 diabetic pregnancies. The three Cesarean sections done in our group of 18 were done for large babies in 2 cases, and for previous section in 1 case.

In deciding on abdominal delivery for a diabetic patient, or for any woman, the operator should weigh well the risk to the mother. In 10 years at this hospital, 1025 Cesarean sections were performed. The maternal mortality from surgical causes, such as hemorrhage, peritonitis, intestinal obstruction and pulmonary embolism was 2.7%, or 1 death in 45 operations. In 10 years in the out-patient department there were 11,608 deliveries which were all normal, low forceps, breech extraction or internal podalic version. The maternal death rate was 1 case in 2902 deliveries. Regardless of diabetes, it is therefore evident that Cesarean section has proved intrinsically 65 times as dangerous to the mother as pelvic delivery. Much thought should be taken regarding the necessity for abdominal delivery in every case, and it should not be selected as an alternative for the normal process of parturition whenever such an outcome may reasonably be expected.

Lactation. The supply of breast milk was insufficient in all of our cases in spite of extra calories added to the diet to compensate for the 500 calories lost daily in the milk. We do not know the explanation of this deficiency. The same phenomenon was found by Markowitz and Soskin in diabetic dogs.

Summary and Conclusions. 1. Under proper management, the diabetic mother may be expected to go through pregnancy and labor safely. Diabetes is usually worse during pregnancy. As a rule there is a sudden decrease in tolerance in the middle trimester which must be compensated by increased insulin. The patient must be checked often during pregnancy. After the pregnancy the insulin requirement returns to the ante-pregnant level.

2. The outlook for the fetus is poorer than in non-diabetics. In the last 4 years, however, the gross and net fetal mortality have been decreased by half.

3. Careful combined medical and obstetrical supervision offers the best outlook for the fetus.

4. The nearest approach to normal delivery is desirable. Cesarean section is reserved for those diabetics whose infants exceed the normal weight, or for cases where some other clear obstetrical indication exists. The two stillborns in our series could not have been saved by more radical delivery. Until we know more about the problem, therefore, we cannot ascribe fetal death to delivery from below, or to over-ripening of the fetus. It is only after we have carefully examined enough diabetic stillborns pathologically that we will have the final answer. For the present, we can find no reason

from our experience to believe that diabetes should be an indication for such a major surgical operation as Cesarean section.

The writers wish to acknowledge the interest and suggestions of Dr. W. R. Ohler.

REFERENCES.

- (1.) Carlson, A. J., and Drennan, F. M.: *Am. J. Physiol.*, 28, 391, 1911. (2.) Carlson, A. J., and Ginsburg, H.: *Ibid.*, 36, 217, 1914-1915. (3.) Folin, O., and Berglund, H.: *J. Biol. Chem.*, 51, 213, 1922. (4.) Johnson, C. R.: *Am. J. Surg.*, 8, 51, 1930. (5.) Markowitz, J., and Soskin, S.: *Am. J. Physiol.*, 79, 553, 1926-1927. (6.) Noorden, quoted by Kleiner, B. F.: *Med. J. and Rec.*, 135, 174, 1932. (7.) Peckham, C. H.: *Johns Hopkins Hosp. Bull.*, 49, 184, 1931. (8.) Skipper, E.: *Quart. J. Med.*, 26, 353, 1933. (9.) Stander, H. J., and Cadden, J. F.: *Johns Hopkins Hosp. Bull.*, 47, 382, 1930. (10.) White, P.: *Surg., Gynec. and Obstet.*, 61, 324, 1935. (11.) Williams, J. W.: *Textbook of Obstetrics*, 6th ed., New York, D. Appleton & Co., p. 601, 1930.

ADENOMA OF THE ISLET CELLS OF THE PANCREAS WITH OPERATION AND RECOVERY.

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THE surgical pathology of hyperinsulinism has been greatly clarified during the past decade. However, as late as 1932, Heyn,² speaking of the treatment of hyperinsulinism, stated that the treatment was medical unless "increasing amounts of carbohydrate became necessary; then surgery, even if unsuccessful, must be tried," and that for the present "surgery appears not to be good enough." Whipple and Frantz⁴ have recently thoroughly reviewed the literature on adenomas of the islands of Langerhans. Although they collected 75 cases of hypoglycemia, in only 29 were tumors of islet tissue found at operation. Hence, these tumors while fully established in the literature are still regarded as relatively rare.

We wish to report an instance of hypoglycemia due to a pancreatic adenoma in which the diagnosis was confirmed at operation, and the patient made a successful recovery. Certain of the observations made on the patient before and after operation are of physiologic as well as clinical interest, in a lesion which is being recognized with increasing frequency.

Case Report. B. F. M., a white male, aged 34, was admitted to this hospital on September 3, 1935, with headache, convulsions and mental disorders as his chief complaints. He has one sister who is insane and another who has asthma. As a past history, the patient gave general good

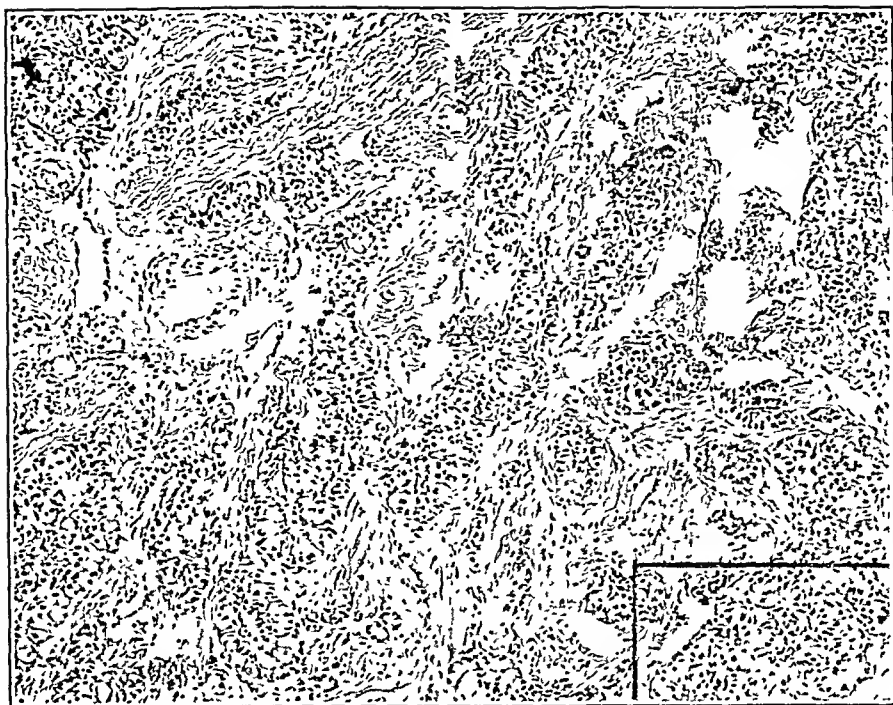


FIG. 1.—Microphotograph of adenoma. $\times 102$.

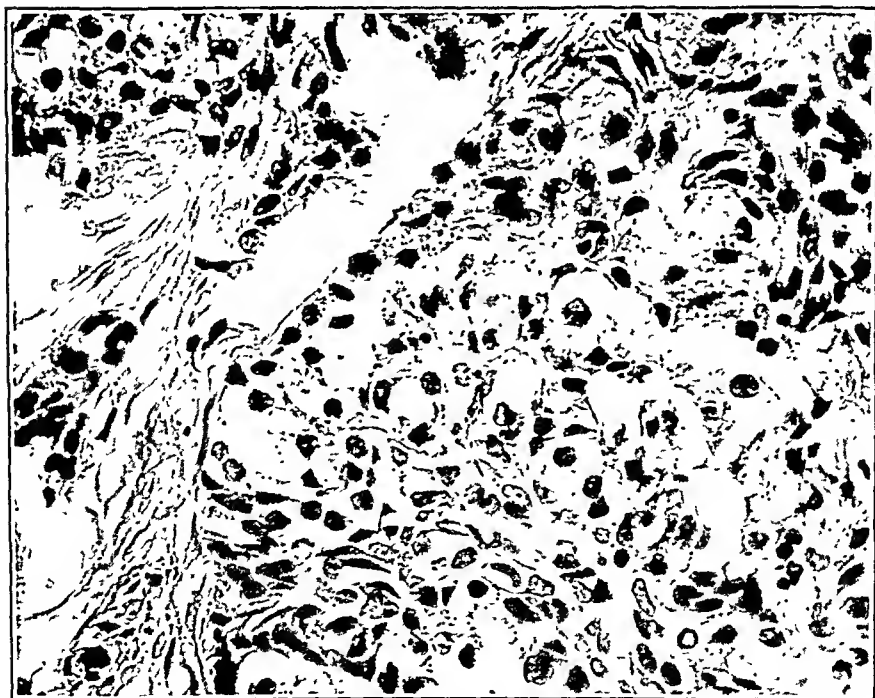
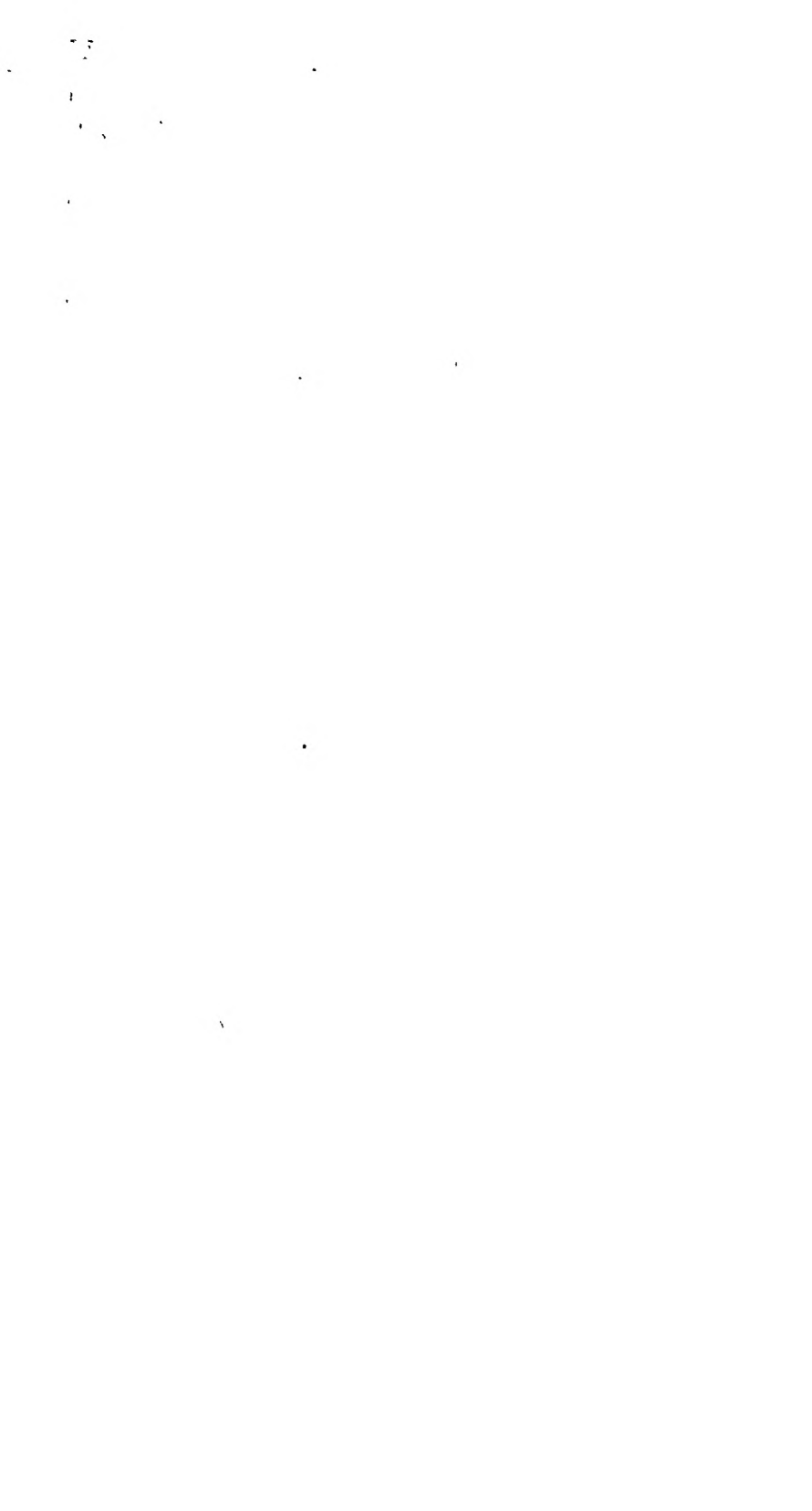


FIG. 2.—Microphotograph of adenoma. $\times 436$.



health with the exception of measles, mumps, chicken pox and diphtheria in childhood. He had an appendectomy at the age of 28. An automobile accident in 1929 caused unconsciousness for 4 hours. He has had asthma and hay fever for the past 5 years. He has never been obese.

Since the middle of July, 1935, he had been having fairly severe, inconstant, headaches. About the same time he had peculiar attacks of mental confusion and disorientation. These included spells of laughter, irrelevant remarks, singing and so forth. It became progressively more difficult to arouse him in the morning. He had had diplopia for 1 day. On August 30, 1935, he went to sleep and could not be roused for 24 hours. When aroused he was quite irrational. Further sleep was followed by a convulsion and vomiting on September 1, and another convulsion occurred September 2, the day before his admission. After this convulsion the blood sugar was 80. He was incontinent of urine September 1 and 2. He was referred to the hospital as a possible case of brain tumor.

Physical Examination. The patient was a tall, well built, well nourished man. On admission he was disoriented, delirious and had hallucinations. Later a wide range of mental symptoms were noted; namely, drowsiness, coma, sullenness and excessive laughter. He never had the slightest memory of any of these episodes after they had passed. Memory was irregular even at best and mental fatigue was noted. For example, stereognosis would be satisfactory for one or two objects, then would fail, but would return after a rest period. There was no evidence of organic neurologic disease. He had a slight fever on admission which led to the tentative diagnosis of encephalitis, but when the spinal fluid was reported negative and the hypoglycemia was discovered he was transferred to the medical ward for study. Here the temperature was 98.2° F.; pulse, 60; respiration, 18; blood pressure, 100/70; and weight, 171 pounds.

There was an occasional extrasystole. The spleen was palpable. Otherwise, physical examination was essentially negative.

Laboratory Findings. Hemoglobin, 103%; red blood cells, 5,600,000; white blood cells, 9700, with a normal differential. Urinalysis was negative. Blood and spinal fluid Wassermann tests were negative. Roentgen examination of the abdomen was negative; the chest showed slight emphysema and increased prominence of the hilum. Blood serum calcium was 10.6 mg. per 100 cc.; serum phosphorus, 3.8 mg.; and cholesterol, 202 mg. The blood sugar findings and the response to various physiologic agents are summarized in Table 1.

TABLE 1.—BLOOD SUGAR STUDIES.

A. Pre-operative.

Procedure.	Fasting.	$\frac{1}{4}$ hr.	$\frac{1}{2}$ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.
1.8 gm. glucose per kg. by mouth	48	175	215	228	175	
Epinephrine 1:1000, 0.6 cc. subcutaneously	89	83	50	75		
Epinephrine 1:1000 1:2 cc. subcutaneously	30	50	98	147				
Insulin—2 units subcutaneously	30	..	25	25	..	30*		

* Symptoms developed and glucose was given after this blood sugar.

B. Postoperative.

1.8 gm. glucose per kg. orally 9 days after operation	98	143	106	87	100	66
Epinephrine 1:1000, 0.3 cc. subcutaneously	78	85	88	88				

During his stay in the hospital several attacks of hypoglycemia were observed in which the response to glucose, administered intravenously and

orally, was dramatic. Pre-operatively he was placed on a high-carbohydrate diet of 6 feedings at 4-hour intervals. He was much improved on this, although a morning blood sugar after several days of this régime was 56.

On September 28, 1935, an excision of the adenoma of the pancreas was done. The abdomen was opened through a long, left upper paramedian incision. An incision was made in the gastrocolic omentum and when the bowel had been packed away and retracted the pancreas was readily exposed. No lesion was visible on the surface but when the lower border of the pancreas was mobilized, upon palpation there was found to be a nodule near the tail on the postero-inferior aspect. This lay in the substance of the gland so that a small incision had to be made into the gland before the tumor could be shelled out, silver clips being used to control the bleeding from the parenchyma of the gland.

The tumor measured approximately 1.5 cm. in diameter and was quite firm in consistency (Figs. 1 and 2). Bleeding from the tumor bed having been readily controlled, the incision in the mesentery was then closed with catgut and the abdominal wall closed in layers with catgut in the muscles and fascia and clips in the skin.

Two cigarette drains were inserted to take care of the drainage from the site of removal of the tumor.

The patient's immediate condition after operation was highly satisfactory. The operation was completed at 10.50 A.M. and he was immediately given venoclysis of normal saline and 5% glucose at a rate of 180 cc. per hour. The blood sugar at 12.15 P.M. was 252 mg.%. During the afternoon the urine contained approximately 3.5% of sugar.

The venoclysis was terminated at 4.30 P.M., but the blood sugar remained elevated, being 194 mg.% at 9 P.M. At 10.15 P.M. the urine sugar was 3.3%. He was given 10 units of insulin at 11.30 P.M., and by 6.30 A.M. there was no sugar in the urine and the blood sugar was 118 mg.%. The fasting blood sugar on September 30, 2 days after operation, was 107 mg.%, and the urine was free of sugar. During this period the pulse rate varied from 50 to 90 and there were frequent extrasystoles. On October 8, 1935, the fasting blood sugar was 93 and, on October 12, it was 78 mg.%. The patient was discharged on October 13, 15 days after operation, with complete relief from his pre-operative symptoms.

The data from various studies made during the postoperative period are given in Table 1B.

Three months after operation the patient was in excellent health, completely relieved of the disturbances which were present before operation. A word may be said about the effect of this operation on the patient's asthma. Prior to operation he had had, as was noted, "moderate asthma and hay fever for 5 years." He had two fairly severe nocturnal attacks of asthma, relieved by 10 minims of adrenalin, before operation. After operation, there were no attacks which required adrenalin or which elevated the respiration. However, ephedrin by mouth was used to relieve very mild asthmatic symptoms.

One year after operation the patient writes that his asthma has not ceased but is much less severe and less frequent. This he attributed to keeping away from certain feathers and dusts known to aggravate it.

Discussion. Seale Harris,¹ in 1924, suggested that the pancreatic islet cells might elaborate an excess of insulin and give rise to hypoglycemia. The symptom complex of the hypoglycemia due to an islet adenoma was not then understood. It is interesting that the 6 cases observed by Whipple and Frantz⁴ personally had been first seen in a neurologic institute where they had gone for nervous and

psychiatric disturbances. It should be stated, however, that the finding of a low blood sugar in association with neurologic or psychiatric symptoms is not sufficient for the diagnosis of pancreatic adenoma.

The patient described had the characteristic mental and nervous symptoms of hypoglycemia, confirmed by the finding of a low blood sugar level at the time of his symptoms. There was temporary response to carbohydrate ingestion and exploration was undertaken with the successful removal of an islet adenoma. The transitory diabetes postoperatively has been observed by others and is presumably a phenomenon of readjustment.

The apparent persistence of asthma after operation is interesting in view of the recent report of Wilmer, Miller and Beardwood⁵ on the relation of blood sugar to asthma. The improvement in allergy noted after 1 year is due to better habits of living and affords no evidence that his allergic condition has been relieved by the operation.

Glucose tolerance, adrenalin and insulin tests were carried out at various times. The features of these tests were a diabetic sugar tolerance curve before operation, a possible resistance to adrenalin and no sensitivity to insulin. The occurrence of a diabetic sugar tolerance curve, while not the common finding, has been noted by others. The effect of adrenalin may have been the result of a tolerance developed through its use by the patient in asthmatic attacks. In stating that there was no sensitivity to insulin, the authors have in mind the patient's failure to develop symptoms until 3 hours after its administration, and his ability prior to this time to remain symptom-free at a low blood sugar level. The dose of insulin used here has produced a prompt effect in such insulin sensitive states as Addison's disease. The response of this patient to insulin is similar to that of a normal animal given a small dose of insulin and is in contrast to the severe convulsions which occur in 40 to 60 minutes after insulin is injected in a hypophysectomized animal (insulin sensitive). One would expect this, namely, that the contrainsular mechanisms would be very active in the presence of an insular adenoma and that this would govern the response to injected insulin.

In reviewing these three tests, which have been commonly applied to patients suspected of insular hyperfunction, several things are apparent. Glucose, adrenalin and insulin all influence the blood sugar and each is intended to test a different aspect of the individual's sugar regulation. It is now recognized that varying conditions under which these tests are made will lead to very divergent results. Thus, in states of liver glycogen depletion, adrenalin can produce little or no response, and yet a similar lack of reaction is observed in the glycogen saturated liver in von Gierke's disease. The same types of uncertain response may be found with glucose

and insulin. In all instances, the response is conditioned more by the liver than by the presence or absence of an islet tumor. The recent work of Soskin,³ showing that the sugar tolerance curve depends on the liver and not at all on the presence of the pancreas, is the most striking demonstration of the fact that alterations of the blood sugar cannot always be regarded as diagnostic of the condition of the pancreas.

It seems then that in these patients the association of symptoms with low blood sugar levels is the criterion which justifies exploration in the event that the symptoms are inadequately relieved by treatment by glucose.

Summary. We have reported the case history of a patient with a pancreatic islet adenoma. The lesion was diagnosed prior to operation and it was removed with complete recovery from the symptoms which it induced. The patient's asthma was not relieved by a return of the blood sugar values to a normal level. Pre-operative and post-operative studies on the effect of epinephrine on the blood sugar and sugar tolerance studies at both stages are discussed.

REFERENCES.

- (1.) Harris, S.: J. Am. Med. Assn., 83, 729, 1924. (2.) Heyn, L. G.: Ibid., 98, 441, 1932. (3.) Soskin, S., Allweiss, M. D., and Cohn, D. J.: Am. J. Physiol., 109, 155, 1934. (4.) Whipple, A. O., and Frantz, V. K.: Ann. Surg., 101, 1299, 1935. (5.) Wilmer, H. B., Miller, M. M., and Beardwood, J. T.: Southern Med. J., 29, 197, 1936.

TUMOR OF THE BRAIN WITH NORMAL ENCEPHALOGRAM.

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As a rule expanding intracranial lesions produce alterations in the size, shape, and position of the ventricles or an obliteration of the subarachnoid air channels on the side of the neoplasm. These changes depend upon the position, size and nature of the expanding lesion. Since there are so many variations in the "normal," the correct interpretation of air films is beset with difficulties.

In a series of 500 tumors of the brain verified at the Mount Sinai Hospital, in which 120 patients had intracranial air injections, 7 showed normal aërograms. Two other instances of negative encephalograms were found among case records of other institutions (1 from Montefiore and 1 from Bellevue Psychiatric Hospital).

In each one of these cases the conclusion that the encephalogram showed no abnormalities was reached after examination of the plates by the neurologist, neurosurgeon and roentgenologist.

In 8 cases the encephalograms were considered normal and in 1 case the ventriculogram was declared negative for tumor.

Case Reports. CASE 1.—S. F., a boy aged 12, complained of occasional attacks of headache, nausea and vomiting for 6 weeks before admission. Twelve days before he entered the hospital, right-sided convulsive movements appeared without any loss of consciousness. Following this attack the patient vomited. These seizures recurred a number of times during the 2 days before his admission.

The examination showed a brachiofacial paresis with pyramidal tract signs on the right side. There was a slight defect in the periphery of the upper quadrant of the right temporal field of vision. The fundi were normal. A lumbar puncture showed an initial pressure of 120 mm. of water. Nine days after admission an encephalogram showed normal size, shape and position of the ventricles and a moderate amount of air in the subarachnoid spaces on both sides. Two weeks after the encephalography a craniotomy was done. A tumor, 3 cm. in diameter was found in the left paracentral lobule. The histologic diagnosis was spongioblastoma multiforme. Two weeks after craniotomy the patient was discharged as improved.

Comment. The diagnosis in this case was based entirely on the clinical findings. Because there were no signs of intracranial hypertension, this patient was subjected to an encephalogram. The negative air studies delayed operative interference until definite progression was noted.

CASE 2.*—A. B., male aged 44, was admitted to the Bellevue Psychiatric Hospital on March 16, 1935, because of mental symptoms. Six months before admission the patient began to complain of vague abdominal pains and headache. Several abdominal laparotomies were performed without relief. Two weeks before admission the headaches became more severe, his vision became blurred and he became irritable and confused.

The examination showed an ataxic gait; bilateral ptosis, more marked on the left side, was present; slight nystagmus on looking to the right and marked upward and downward impairment of conjugate gaze were noted. The pupils were equal and slightly irregular, though they reacted to light and in accommodation. There was some cogwheel rigidity in the right upper limb. The fundi were negative. He was lethargic, bewildered and confused. The lumbar puncture showed a normal pressure, clear and colorless spinal fluid with 27 lymphocytes per c.mm. Eleven days after admission an encephalogram showed normal ventricular and subarachnoid systems. The patient became progressively worse and stuporous, and died 1 month after admission.

The autopsy disclosed no evidence of increased intracranial pressure. The ventricular system was normal. There were apparent softenings of the tip of the left corpus striatum, the right globus pallidus, the median portion of the putamen and in the substantia nigra. No other gross lesions were found. Sections through these areas showed an unclassified primary tumor of the brain, probably of the nature of a sarcoma. The tumor tissue was infiltrating and invaded the basal ganglia and the floor of the third ventricle.

* This case report is published through the courtesy of Dr. K. M. Bowman, Director, Bellevue Psychiatric Hospital.

Comment. This case illustrates the presence of a normal ventricular system not only by encephalogram but at autopsy. The interesting feature is the presence of an infiltrating tumor without evidence of intracranial pressure in the region of the floor of the third ventricle and aqueduct where one would expect an early obstruction to the flow of the cerebrospinal fluid.

CASE 3.—W. A., a man aged 50, was admitted to the Mount Sinai Hospital with a history of convulsive seizures for 26 months. During this period he became more irritable and quarrelsome. Seven months after the onset of his illness he was considered a "brain tumor suspect" in another hospital. An encephalogram at that hospital revealed a slight increase in the subarachnoid spaces. This suggested a degenerative process at the time. The ventricular system and the basal cisterns were declared to be normal. Because of the relatively negative encephalogram, he was discharged with the diagnosis of encephalitis. Two weeks after discharge and 18 months before his admission to the Mount Sinai Hospital he had "hives" and then developed twitchings in the left side of the body followed by a progressive left hemiparesis. For the last 6 months before his death he noted that when he grasped an object with his left hand he could not release the object at will.

The examination at the Mount Sinai Hospital revealed definite euphoria, a left spastic hemiparesis, and a left forced grasping reflex. The fundi were normal. An encephalogram showed a shifting and distortion of the ventricular system due evidently to a tumor in the right parasagittal region. An exploratory craniotomy disclosed a glioma the size of an orange in the right paracentral lobule.

Comment. The slight increase in the subarachnoid markings, if pathological, was not caused by the proven expanding lesion. This patient was under constant observation by many excellent neurologists and roentgenologists. (During the earlier stages of a brain tumor the aërogram may be negative.)

CASE 4.—C. B., a male aged 38, was admitted to the Mount Sinai Hospital with the main complaints of headache and a speech disorder. Sixteen months before, following a brief prodromal period of headache and dizziness, he had a convulsion with very transitory impairment of speech. Five months later a left facial paralysis appeared. This persisted for 2 weeks. The patient was well again up to 4 months before admission when he had a fleeting attack of dizziness and unsteadiness in gait. Two months later he complained of vague gastro-intestinal distress and headache. This was soon followed by difficulty with speaking and an inability to understand what was said to him. The speech impairment became worse and he soon began to fear that someone would harm him. He was anxious and restless. Severe headache with frequent nausea were present throughout the illness. He again improved and became symptom-free until 1 week before admission when all symptoms reappeared.

The examination showed a slight right lower facial weakness. The fundi were normal. The patient was spontaneously overtalkative, and appeared frightened. Lumbar puncture showed a normal initial pressure. The clinical impression was that of a tumor in the left temporal lobe. During his residence in the hospital he improved. Two weeks after admission he was discharged to the care of his family physician.

Three weeks later he was readmitted because of severe headaches and inability to recall names of simple objects. Examination this time showed



FIG. 1.—Normal encephalogram with verified brain tumor. Case 2.

slight tremor of both hands, a suspicious left Babinski and a right lower facial weakness. He was confused; his memory for recent events was poor; there was an anomia; he was unable to do simple calculations and he found it difficult to obey complicated commands. A right homonymous hemianopsia was noted on perimetric examination.

Because of the complete remissions and exacerbations the patient was thought to be suffering from an aneurysm. A Roentgen ray of the skull revealed a calcified pineal gland in the normal position. The anterior clinoids of the sella turcica were slightly eroded. One week after admission an encephalogram showed large globular collections of air in the subarchnoid spaces but no air in the ventricles. Four days later the hemianopsia disappeared and 8 days after the encephalogram a ventriculogram was performed and showed normal size and position of the ventricular system. The patient continued to improve and on discharge 6 weeks after his admission all examinations gave negative results.

Six months after leaving the hospital the patient was readmitted because of an attack of tremulousness, recurrent confusion, inability to speak and a convulsive seizure. On the day following this admission a ventricular puncture was performed. No fluid could be obtained from the left side. Two days later no tumor was found during a left exploratory craniotomy. The autopsy disclosed a granular round mass 3 cm. in diameter in the region of the left angular gyrus. This tumor proved to be a cavernous angioma.

CASE 5.—I. M., a man aged 30, was admitted to the Mount Sinai Hospital with a history of a head tremor for 15 years. In addition, twitching of the limb on the left side was reported for 8 years. Five years before admission a grand mal seizure was observed for the first time. These convulsive seizures recurred and were frequently precipitated by undue mental strain or emotional stress.

The examination showed a mild left lower facial weakness with diminished sensation on the left side of the body. The left knee jerk was slightly more active than the right. The fundi and visual fields were normal. Eight days after admission an encephalogram was performed and an irregular calcified mass was found to be situated 1 inch behind the coronal suture on the right side near the dura. The ventricles were found to be symmetrical and uniformly slightly enlarged but there was no shift. The subarachnoid spaces and the basal cisternæ were normal. The patient left the hospital against advice. One year later a Roentgen ray of the skull showed the calcified mass to be slightly larger than on the previous examination. A calcified pineal was found in its normal position. There was no evidence of increased intracranial pressure. Except for a questionable bilateral early papilledema the physical findings were the same as those on the previous examination. An exploratory craniotomy was subsequently performed and a calcified tumor was removed from the right parietal lobe. Histopathologically, the tumor was a calcified glioma.

Comment. Normal ventricular and subarachnoid systems existed during the course of a brain tumor with definite calcification which increased in size during the course of observation. Slight symmetrical dilatation of the ventricles has questionable pathologic significance.

CASE 6.—L. Z., a 39-year-old housewife, entered the Mount Sinai Hospital complaining of headache. Two years before admission she experienced intense generalized headaches. Seven months before admission, after a mentally retarded son was sent to an institution, she became worse. She was depressed and lost interest in her surroundings. She had recurring

periods of confusion. After 2 months these mental changes cleared up. Two months before admission the mental symptoms reappeared. One month later weakness of the left upper limb set in, to be followed in a few days by the feeling that someone was sitting at her left side and that she was holding something in her hand.

The examination revealed a slow, cautious gait with decreased associated movements of the left upper limb; the left palpebral fissure was slightly greater than the right; the left pupil reacted *consensually but was fixed to direct light*; the fundi showed early papilledema, more marked on the left side; she was dull; psychomotor retardation, confusion, defective memory and emotional instability were present. The mental picture was that of an organic psychosis. A Roentgen ray of the skull was negative. The lumbar puncture showed xanthochromic fluid under an initial pressure of 160 mm. of water with 40 lymphocytes per c.mm. and a total protein of 270 mg. per 100 cc. Twelve days after admission the encephalography showed a normal ventricular system. The subarachnoid spaces were not visualized well on either side. A few days later the patient left the hospital against advice. An encephalogram performed 1 month after discharge showed the ventricular system to be displaced to the right and a craniotomy revealed a left parietal lobe glioma.

Comment. This case illustrates the fact that a patient with a tumor of the brain may have papilledema and at the same time a normal ventricular system. The clinical diagnosis was tumor of the brain but there were insufficient signs for localization. Since the aërogram was negative for tumor, operation was delayed until a subsequent encephalogram showed a shift of the ventricles to the right. The decreased amount of air in the subarachnoid spaces on both sides may be considered a normal variation.

CASE 7.*—B. K., a male aged 45, was admitted with the chief complaints of stiffness and weakness in the right arm and leg. For 18 years before admission, the patient had suffered with severe frontal headaches. In 1922, 12 years before admission, the right upper extremity suddenly became weak. Following this episode, the right side of the body became progressively weaker. During the last year before admission there were a few convulsions. He became emotionally labile, depressed and irritable.

The examination showed a right hemiparesis with motor aphasia. The fundi were normal. An encephalogram done at another hospital revealed a slight uniform dilatation of the entire ventricular system. A definite diagnosis could not be made. The patient was discharged for observation. One year later, the patient was readmitted with bilateral papilledema. The encephalogram on this occasion showed a slight shift of the ventricular system to the right with an obscuration of the left inferior horn. Craniotomy and subsequent autopsy disclosed a vascular tumor (hemangioendothelioma) in the region of the left corpus striatum, hippocampus and island of Reil.

Comment. The operation was delayed because there was no evidence of an expanding lesion by encephalogram. A slight dilatation of the ventricular system is frequently found in conditions other than tumor and as previously stated may be considered a normal variation.

* This case report is published through the courtesy of Dr. S. P. Goodhart, Attending Neurologist, Montefiore Hospital.

CASE 8.—A. C., a 42-year-old housewife, was admitted to the Mount Sinai Hospital with the history of recurring attacks of dizziness, nausea, and fainting since her 23d year. Attacks of mild headache had also been present. These complaints were attributed to a head injury sustained 13 years previously. At the age of 32 "she was operated on the left side of the head." She improved, and for 8 years was symptom-free. Two years before admission the fainting spells recurred; 6 weeks before admission vision became impaired and 3 weeks later she had a generalized convulsion.

The examination showed bilateral papilledema with hemorrhages, generalized hyperreflexia, and a positive left Babinski. A Roentgen ray of the skull showed an old trephine opening in the left parietal bone.

An encephalography was unsuccessful. A few days after this air injection the patient became stuporous, and an emergency right subtemporal decompression was performed. The result was a remarkable improvement with almost complete recession of the papilledema.

She was discharged as improved and was in good health for 10 months. She then suddenly became comatose. This was followed by a transitory right hemiparesis. The examination on the second admission revealed low grade bilateral papilledema and a positive left Babinski. Smell was impaired bilaterally. Under observation she had a generalized convulsion. An encephalogram revealed normal ventricles and subarachnoid spaces. Since the suspected tumor could not be definitely demonstrated, the patient was discharged to the Follow-up Clinic. She was watched there for 2 years. Convulsive seizures recurred about every 3 months. Impairment of memory became more marked during the year before her last admission.

When she was readmitted a third time, 3½ years later, the only objective signs were a slight blurring of the right optic disc margin and bilateral hyposmia. A third encephalogram showed a questionable shift of the ventricular system to the left side and a shadow which was interpreted as a calcification in the right subfrontal region. Because of this calcific shadow the right frontal lobe was explored and a hemangiomatous tumor involving two-thirds of the right pre-frontal lobe was excised.

Comment. It was difficult to understand the existence of choked disks in the presence of a normal ventricular and subarachnoid system. Despite the fact that the patient had had bilateral subtemporal decompressions, changes in the ventricular system should be expected where papilledema existed.

In this case, the excessively long remissions in symptoms, the absence of headache, the paucity of physical signs, and negative air studies, all tended to exclude an expanding intracranial lesion, although the total impression of the clinical picture and the course of the disease pointed to what proved to be the correct diagnosis.

CASE 9.—S. H., a male aged 59, entered the Mount Sinai Hospital with a 4-months' history of convulsions. Fifteen years before admission a hemangioma of the lower right lip was excised but had recurred. The present illness began 4 months prior to admission when the patient suddenly became aware of a clonic twitching of the left side of the body which began in the left wrist and spread upward to involve the whole left side of the body. Following this attack the left side of the body was paralyzed for 2 hours. There were numerous similar attacks since the onset of the present illness.

The examination revealed a spastic paralysis of the left arm and a flaccid paralysis of the left leg with tendon hyperreflexia, absent abdominals and

loss of plantar flexion on the same side. The fundi were normal. The blood pressure was 160/100. The lumbar puncture showed an initial pressure of 160 mm. of water. He was depressed and anxious.

The clinical diagnosis was tumor of the right frontal lobe. Five days after admission a right frontoparietal exploratory craniotomy was done but no tumor was found. Two weeks following the operation an encephalogram was performed during which 110 cc. of fluid were removed and 90 cc. of air injected. Both ventricles were found to be normal in size and shape. There was a question whether the right lateral ventricle was on a slightly lower level than the left. The third ventricle was normal in size and position. The diagnosis of an expanding lesion could not be made after examination of these aërograms.

The patient continued to improve. The left hemiplegia disappeared almost entirely. Twenty days after the craniotomy he was discharged from the hospital with instructions to return if any new symptoms appeared. Despite the negative encephalogram and improvement in symptoms the provisional diagnosis was right frontal lobe tumor.

Seventeen days after his discharge from the hospital the patient was readmitted because of right-sided headache, restlessness, retention of urine and increasing stupor. The examination on this admission revealed the same positive findings as during his previous residence in the hospital. Eight days later the patient was reexplored. A transitional cell glioma (6 by 4½ by 3 cm.) was removed from the right paracentral lobule. Two weeks after operation the patient was discharged from the hospital. He died at home 3 months later. No autopsy was obtained.

Comment. The diagnosis of tumor of the brain on admission was based on a clinical course. Since the first exploratory craniotomy revealed no tumor, an encephalogram was performed for more precise localization. This was of no aid. The slightly lower position of the right ventricle probably had some significance but it was insufficient to warrant a confirmatory diagnosis of the presence of a tumor, even after a consideration of the clinical history in this case.

Tumors of the brain, irrespective of their location, nature, size and rate of growth, may exist for a long time without significant alterations of the ventricular and subarachnoid spaces. In this group, the locations of the neoplasms were as follows: 3 were in the parietal lobe, 4 in the frontal lobe, 1 in the corpus striatum and temporal lobe and 1 in the basal ganglia. The histologic nature of the tumors was as follows: 3 hemangiomata, 5 gliomata and 1 sarcoma. The duration of the course of the disease up until the time a normal encephalogram was found varied from 2 months to 19 years. In most instances the course was protracted. In 4 cases papilledema was found to be present while the ventricular system was normal. In 8 cases the operation was delayed because the encephalogram was normal. In 9 cases the clinical signs were sufficient for localization and diagnosis of tumor. Two patients showed calcifications in the tumor in the presence of "normal" encephalograms. One patient had a normal encephalogram and at autopsy normal ventricles, despite the fact that the tumor was located in the corpus striatum.

The wider use of air injections for the diagnosis of intracranial

disease and the recent emphasis on the importance of early diagnosis of tumor of the brain will undoubtedly lead to the more frequent finding of normal encephalograms in cases of brain tumor.

The literature on this subject is extremely meager. Dahl-Iversen¹ reported a case of papillomatous tumor of the fourth ventricle with papilledema and with a normal aërogram after ventriculography. The autopsy confirmed the absence of dilatation of the ventricular system. We have not been able to find other cases.

The interpretation of slight variations in the aërogram is beset with difficulties because of the relatively frequent incidence of such deviation from the accepted normal. It is doubtful whether slightly diminished subarachnoid markings or a mild indentation or diminution in size of a ventricle will by and in itself justify exploration. A slight depression was found in the anterior part of the left lateral ventricle in Dahl-Iversen's case though the tumor was in the posterior fossa. Goette² has collected the known information on the variations of the normal aërogram. He concludes that there are many abnormalities which are within normal limits. Kornblum and Grant³ state that: "Encephalograms performed upon the same individual at different times under apparently normal conditions may vary markedly in the size and shadows representing the subarachnoid spaces." Slight variations assume significance only when the clinical findings suggest an expanding lesion in a particular part of the brain.

It must be distinctly understood that the designation "normal" depends on the concept of normalcy of the aërogram at the time of the diagnosis. It is likely that further study of the encephalogram in tumors will reveal significant changes the importance of which has been overlooked.

Summary. 1. A series of 9 cases of brain tumor with normal aërograms is reported.

2. Normal ventricular and subarachnoid systems may exist irrespective of the nature and location of the tumor and the duration of its course.

3. Attention is called to the fact that a negative encephalogram does not exclude the diagnosis of a tumor based on clinical grounds.

4. During the earlier stages of a brain tumor the aërograms may be negative.

REFERENCES.

- (1.) Dahl-Iversen, E.: *Lyon Chirur.*, 81, 689, 1934. (2.) Goette, K.: *Deutsch. Ztschr. f. Nervenheilk.*, 110, 9, 1929. (3.) Kornblum, K., and Grant, F. C.: *Am. J. Roent.*, 32, 311, 1934.

VISCERAL PATHOLOGY IN MEASLES.

A CLINICO-PATHOLOGIC STUDY OF 100 FATAL CASES.

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MEASLES has long been recognized as a serious and frequently fatal disease, and the pathology of this condition has been the object of much study and investigation. Most of the studies, however, have concentrated on one organ or group of organs, particularly the respiratory tract and the nervous system. This is an attempt to study the general pathology found throughout the body in a large series of measles deaths. It consists of 100 autopsies, 94 from the laboratory files—3 previously reported^{5,8,10}, and 6 personally performed. For most of those on file, it was difficult to give satisfactory gross descriptions; accordingly, the references to the gross pathology are for the most part brief quotations, the chief emphasis being placed on microscopic findings.

Pathologic Anatomy. *Heart and Pericardium.* Pericarditis was present in 4 cases. Two showed a shaggy exudate on the visceral pericardium with the pericardium distended with purulent fluid, while 2 had lesser amounts of purulent fluid and no fibrinous exudate. Pericardial effusion was somewhat more common, 13 cases showing effusion of clear fluid, 3 of 50 cc. or over and 10 of 15 to 50 cc. The heart itself showed no characteristic gross changes. Dilatation of the right heart in varying degree was found 24 times.

Of 91 hearts examined microscopically, only 4 showed more than the usual toxic changes. These 4, including the 2 with exudative pericarditis, had cellular infiltration of the myocardium. The infiltration was chiefly lymphocytic, and was partially, but not predominantly, perivascular in distribution.

Pleura. Involvement of the pleura was noted in 27 cases. Empyema occurred in 13, 2 bilateral and 11 unilateral. A well marked fibrinous pleuritis, excluding those cases showing only a few fresh fibrinous strands, was found in 14 cases, 5 with serous effusion and 9 without effusion. Bilateral pneumothorax, with associated bullous emphysema of the anterior mediastinum, was seen once, death having occurred 4 hours after a tracheotomy.

Lungs. Pneumonia of sufficient extent to be recognizable grossly was present in 93 cases. Of the 7 showing no gross pneumonia, 3 also had none by microscopic examination, and 3 only a mild incipient process. The gross process had mostly a patchy lobular distribution.

Microscopically, the process was chiefly of 2 types. The interstitial type, the more usual, consisted of a marked thickening of the bronchial and alveolar walls, with a thin exudate of serum and

phagocytes in the alveolar lumina. The lobular type showed a heavy purulent exudate, consisting almost entirely of neutrophils and fibrin, with distention of the alveoli and consequent thinning of their walls. The bronchi and bronchioles in almost all the sections in both classifications contained purulent exudate. This, as a rule, did not invade the walls, although the epithelium usually exhibited a catarrhal desquamation, indicating the presence of an acute bronchitis and bronchiolitis. The bronchial walls were for the most part intact, although there was usually some slight peribronchial lymphocytic infiltration.

In most instances both types were present, but often one or the other greatly predominated. The predominating variety was interstitial in about one-half of the cases and lobular in about one-sixth, while the remainder had a fairly equal distribution of both varieties. The earliest cases were of the peribronchial interstitial type.

The most unusual lung finding was in a case in which death was apparently caused by a large infarction of the right upper lobe. The lesion proved to be due to complete occlusion of the branch of the pulmonary artery supplying this lobe by pressure from several enormously enlarged, non-tuberculous lymph nodes.

Larynx. The larynx in practically all cases showed slight to moderate congestion and edema, but in 13 the changes were excessive. Of these, 9 presented an extremely severe laryngitis, 6 showing ulceration (involving the vocal cords in 3), and 3 a membrane. The remaining 4 cases, though without membrane or ulceration, had sufficient congestion and edema to cause respiratory difficulty and death from obstruction.

Microscopically, sections were available in 4 of these severe cases. All showed an acute inflammatory process, with thrombi in the veins and large deposits of fibrin, and in 3 the inflammatory changes were widespread, the fibrin deposition being even more pronounced in the deeper layers than on the surface.

Of these 13 cases, it is of interest that 8 were typical cases of measles croup, with death clinically due to laryngeal obstruction. Two had no note on the chart concerning a laryngeal inflammation, while 3 had only mild clinical laryngitis. Of the 13, nose and throat cultures were negative for Klebs-Loeffler bacilli in 9, while in 4 there were no nose and throat cultures reported.

Trachea. The trachea and primary bronchi were almost uniformly deeply injected, with a reddened mucosal surface and usually a mucoid secretion. No membrane was observed, other than in the upper few centimeters as a direct extension from a laryngeal membrane. Microscopically, the usual picture was an intense congestion of the mucosal vessels, and a mild lymphocytic infiltration, usually involving neither the epithelium nor the glandular layer but diffusely infiltrating the area between. Of the 22 sets of sections

examined, 13 were of the type just described, while 9 ranged from slightly greater inflammatory change with some invasion of the glands to a severe inflammation with necrosis and epithelial sloughing.

Thymus. Satisfactory figures on the gross appearance of the thymus could not be compiled, but the striking feature of this gland was the microscopic picture. Of sections from 64 cases, 41 showed a marked degree of atrophy with great depletion of the lymphoid tissue. In 34 the Hassall's corpuscles were either greatly decreased in number or entirely absent, while in the remaining 7 there were numerous large corpuscles undergoing marked degeneration. Lymphoid hyperplasia was found only twice. This atrophic process is apparently the so-called accidental involution which is said to occur in many acute infections, and which has been seen in this laboratory in other contagious diseases.

Tonsils. The tonsils were for the most part enlarged and inflamed, but actual gross purulent inflammation was seen in only 2 cases. Microscopically, these 2 were the only ones to show an acute inflammatory process. In both, blood-vessels were seen to pass directly through areas of acute inflammation, and in 1 of them the vessel wall was necrotic, with actual invasion by cocci visible (Fig. 1). There was marked generalized sepsis in both cases, with hemolytic streptococci cultured throughout the body, including tonsils and heart's blood, and the microscopic picture would seem to provide an excellent illustration of the probable portal of entry. Giant cells, as described by Warthin and others^{2,6,7,11} in the tonsil and appendix in the prodromal stage of measles, were not found in either organ in our material.

Lymph Nodes. The lymph nodes throughout the body were enlarged and congested, particularly those in the cervical, peribronchial and mesenteric groups. Only 3 showed suppuration. The characteristic microscopic picture was one of *subacute* inflammation. In contrast to the lymphoid hyperplasia in the spleen and intestinal tract, the lymphoid tissue of the nodes seemed decreased in amount, with relatively little lymphoid activity. The vessels were congested, and the sinuses widely dilated and packed with lymphocytes, large phagocytic mononuclear cells, and plasma cells. Fibrin was occasionally seen. Definite *acute* inflammation was observed in only 2 of the 77 sets of sections studied. Extreme congestion was found in 8 cases, 1 of which also showed extensive microscopic hemorrhage. Lymphoid hyperplasia was observed only twice. A mild hyperplasia of the reticulo-endothelial system was not uncommon.

Spleen. The spleen in most instances was considerably enlarged. The characteristic gross appearance was one of marked congestion and follicular hyperplasia; much less often a soft, mushy, septic spleen was found. Microscopically, the typical picture was one of

marked congestion with lymphoid and reticulo-endothelial hyperplasia. Microscopic hemorrhage was seen in 14 cases (marked in 2).

Liver. The liver was generally enlarged, and usually showed gross evidence of cloudy swelling and congestion. Microscopically, the liver sections uniformly showed toxic changes in varying degree, consisting of cloudy swelling, fatty infiltration, and congestion. The congestion was usually marked, but in only 3 instances was there passive congestion to the point of central necrosis of liver cells. The most frequent lesion observed was an infiltration of the portal spaces with lymphocytes (Fig. 2); this was found in 20 cases (22% of those examined). In 11 it was classified as slight, in 8 as moderate, and in 1 as marked. The infiltration did not in any case invade the liver lobules, and was composed almost exclusively of lymphocytes and rare plasma cells. In none of the sections was there a consistent perivascular or periductal arrangement of the invading cells.

Pancreas. No gross lesions were observed in the pancreas. Microscopically, one section of the 74 examined showed a slight, rather diffuse infiltration of the interstitial septa with lymphocytes and plasma cells.

Adrenals. Marked unilateral medullary hemorrhage was found in 1 case. The adrenals were otherwise grossly normal throughout the series. Microscopic medullary hemorrhage was observed in 3 cases, though only in the one just noted was it extreme. Lymphocytic infiltration of the medulla occurred in 3 sections of the 84 examined.

Kidneys. Grossly, the kidneys generally showed congestion and often cloudy swelling. Mild pyelitis and ureteritis occurred in 2 cases, unilaterally in 1 and bilaterally in the other. Microscopically, practically all the cases showed congestion, and also fairly marked cloudy swelling of the tubular epithelium. Of the 95 sections examined, there was a moderate interstitial mononuclear infiltration in 6, without involvement of the glomeruli (Fig. 3). The cells were chiefly lymphocytes, with a considerable number of plasma cells and cells of endothelial character. Both cortex and medulla were affected. In only 3 cases of the 95 was there any evidence of glomerulitis, and in all of these the process was an early one.

Gastro-intestinal Tract. Acute appendicitis was found in 3 instances, 1 with perforation. No other significant gross changes were noted. Microscopic sections of the gastro-intestinal tract were available in only 14 cases, and beside a single appendix section which showed an acute inflammatory process and no giant cells, exhibited only a moderate intestinal lymphoid hyperplasia in slightly over half the cases.

Peritonitis. Peritonitis was found in 5 cases, 3 of which yielded hemolytic streptococcus on culture. A fourth case was due to a

ruptured appendix, and in the remaining 1 the process was limited to the pelvis and was apparently a tuberculous peritonitis.

Brain, Ears and Mastoids. In practically all of the 29 cases in which the skull was opened, the brain showed moderate edema and congestion, and in 5 there were scattered punctate hemorrhages. A cortical abscess, apparently secondary to mastoiditis, occurred once. Purulent meningitis was found in 3 cases, 2 due to hemolytic streptococci. Serous meningitis with opalescent fluid occurred twice, and hemorrhagic softening due to cortical venous thrombosis was seen once.

Otitis media or mastoiditis or both were found at autopsy in 13 of these 29 cases, involving the middle ear alone in 4, the mastoid alone in 3, and both middle ear and mastoid in 6. Sinus thrombosis was found in 4 cases, 3 of these showing an associated mastoiditis.

Microscopically, toxic changes were generally found in the brain, consisting of congestion, pericellular and perivascular edema, and some degree of degenerative changes in the nerve cells. In 5 cases these changes were especially marked, with small hemorrhages into the Virchow-Robin spaces, and perivascular infiltration with mononuclear cells, chiefly lymphocytes, in 1 instance with very definite cuffing (Fig. 4). These 5 cases were interpreted pathologically as early encephalitis, and in 4 of them a clinical diagnosis of encephalitis was made, while such diagnosis was not made in any other cases. No definite demyelination was found.

Skin. Skin sections were examined microscopically in 11 cases. The only constant finding was slight to moderate lymphocytic infiltration of the corium, sometimes perivascular in distribution, but not uniformly so. Active desquamation of the epidermal cells was occasionally observed. In no instance was there thickening of the cornified layer. Swelling of the endothelial lining cells of the capillaries was noted in 3 sections, and slight subendothelial lymphocytic infiltration in 1. No relationship could be made out between the extent of the microscopic lesions and the appearance and duration of the rash.

Bacteriology (See Table 1). One or more cultures were taken from 74 cases. The most striking feature was the overwhelming predominance of hemolytic streptococci. These organisms were present either alone or with other organisms in 57 cases, or 77% of those from which cultures were taken, and in pure culture, as the only organism found in the body, in 30 cases or 41%. Blood cultures were not taken during life from the majority of the cases, but of the 31 showing a pure hemolytic streptococcus in the heart's blood at autopsy, 5 had similar ante-mortem blood cultures. The only other organisms found in more than one or two cultures were *Pneumococcus*, Types I and XIV, *Strep. viridans*, and *Staph. aureus* and *albus*.



FIG. 1.—*Tonsil*. Acute tonsillitis in measles. Necrotic area with necrosis of blood-vessel. Phloxin methylene blue. $\times 110$ (Under oil immersion, penetration of cocci through the necrotic wall into the lumen of the vessel can be seen.)

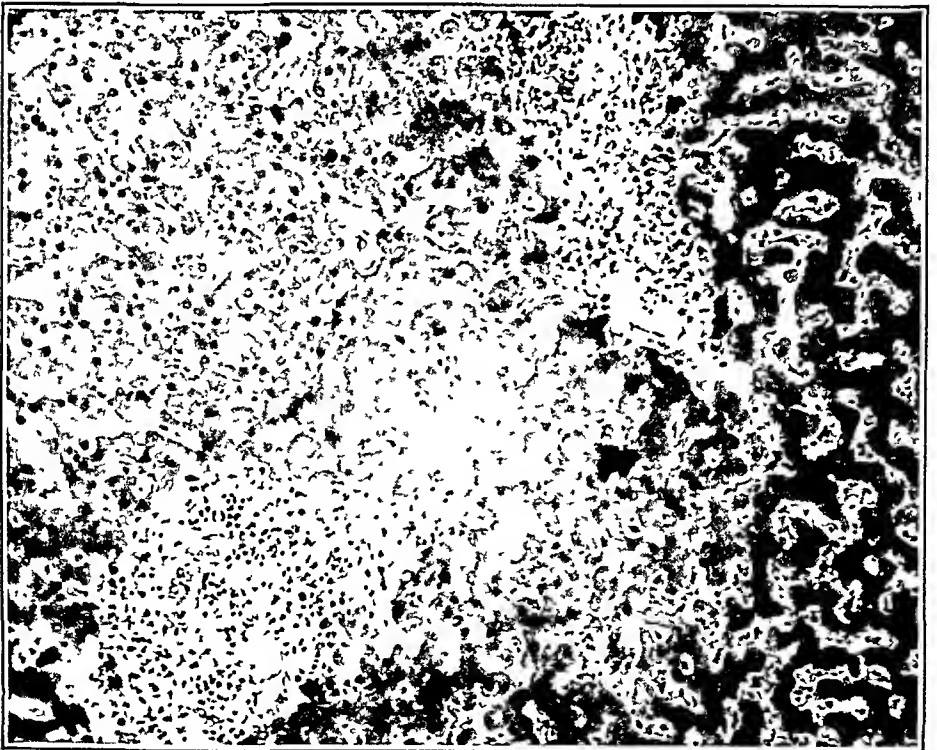


FIG. 2.—*Liver*. Lymphocytic infiltration of portal spaces. Phloxin methylene blue. $\times 135$.



FIG. 3.—*Kidney*. Interstitial infiltration with lymphocytes. Phloxin methylene blue. $\times 150$.



FIG. 4.—*Brain*. Measles encephalitis. Perivascular cuffing. Hematoxylin phloxin. $\times 215$.

TABLE 1.—BACTERIOLOGIC FINDINGS.

	Heart's blood.	Lung.	Chest fluid.	Pericardial fluid.	Peritoneum.	Larynx.	Tonsil.	Testis.	Brain.	Cerebral fluid or exudate.	Spinal fluid or exudate.	Middle ear.	Mastoid.
Number of cultures taken . . .	68	40	15	3	8	4	2	1	3	3	2	3	5
No growth	16	7	1	..	1	1	..	1
<i>Streptococcus hemolyticus</i> . . .	31	21	6	..	2	2	1	1	1	1	1	2	3
<i>Strep. hem. and Strep. viridans</i> . .	4	3	3	1	2	2	1
<i>Strep. hem. and Staph. aureus</i> . .	4	1	..	1	..
<i>Strep. hem. and Green. strep.*</i> . .	1	3
<i>Strep. hem. and Pncumo., Type XIV</i>	1	..	1	1
<i>Streptococcus viridans</i>	1	2
<i>Pneumococcus, Type I</i>	1	1	1	1	1	1
<i>Staphylococcus albus</i>	2	3
Miscellaneous†	8	..	3	1	1	1	1

* Green streptococcus, bile solubility test not done.

† Includes single organisms and groups of organisms not occurring in more than two cultures. These include, in addition to the organisms listed above, *Pneumococcus*, Types II and IV, Pfeiffer's bacillus, *Streptococcus anhemolyticus* (gamma), and *Bacillus coli* (in a case of ruptured appendix).

Clinical Considerations. The age incidence is shown in Table 2. The greatest incidence was in the 18 months period from the sixth month through the second year, 60% falling within this age group. No case occurred under the age of 3 months, and only 2 under 6 months. Only 3 cases were over the age of 8 years, including 1 adult of 40.

TABLE 2.—AGE INCIDENCE.

Under 1 year	21	<i>Under one year:</i>	
12 to 18 months	24	3 months	1
18 to 24 months	17	5 months	1
2 years	11	6 months	1
3 years	7	7 months	3
4 years	7	8 months	5
5 years	2	9 months	5
6 years	4	10 months	1
7 years	2	11 months	4
8 years	2		—
10 years	1		21
15 years	1		
40 years	1		

The incidence of the chief complications, the day of illness on which they were first diagnosed clinically, and the day of illness on which death occurred are summarized in Table 3. It will be noted that pneumonia was an early complication, occurring in 32 cases by the fifth day, and in 71 cases on or before the tenth day. Laryngitis and encephalitis were also found early in the illness, while empyema, as might be expected, was a considerably later complication. Death usually occurred late in the disease, 77% dying later than the first week. No correlation could be made between the day on which death occurred and the character and extent of the lesions found. Tuberculosis as an incidental finding was seen in 3 cases.

TABLE 3.—DATE OF CLINICAL ONSET OF CHIEF COMPLICATIONS.

Day of illness.	1st.	2d.	3d.	4th.	5th.	6th.	7th.	8th.	9th.	10th.	11-15.	16-20.	21st and over.	Not diagnosed clinically.
Pneumonia*	1	3	6	11	11	13	3	11	8	4	8	3	2	7†
Empyema‡	2	5	2	..	3
Laryngitis	..	1	1	2	3	1	2	1	2
Peritonitis	..	1	3
Encephalitis	..	1	1	..	2	1	1	..	3
Meningitis	2	3
Day of death	2	3	3	6	9	7	4	10	21	14	21	

* In 2 cases, pneumonia antedated the onset of measles by 2 and 3 days, respectively.

† On the basis of gross pneumonia at autopsy.

‡ One case of empyema died in ambulance on 10th day of illness and was not admitted. Date of onset of empyema not known.

Discussion. In analyzing the pathologic findings in these hundred cases, the most striking observation is the absence of any specific gross or microscopic pathological lesion which, in the absence of additional clinical data, could lead to a diagnosis of measles. The most constant pathologic change appears to be pneumonia and inflammation of the upper respiratory tract, but even the pneumonia is not of a single type. Elsewhere the gross picture is one of secondary infection and concomitant toxic changes, the infection being most often apparently of a streptococcal nature. Microscopic examination also shows evidence chiefly of a severe and widespread toxic and infectious process. Among these changes, the frequent presence of an interstitial, mononuclear cell infiltration is of especial interest.

Brody and Smith,¹ in a study of the microscopic visceral pathology of a series of scarlet fever cases at this hospital, were particularly impressed by the repeated occurrence of an almost characteristic lesion found in various organs. This consisted of an interstitial round-cell infiltration (predominantly lymphocytic, but also containing plasma cells and other round cells). The infiltration tended to be perivascular in distribution, and practically never affected the specific structures of the organs, such as liver lobules or kidney glomeruli or tubules. They concluded that the process was most probably the result of a circulating streptococcus toxin, as the interstitial lesion is seen in other infectious diseases, notably diphtheria and measles, but always with an associated streptococcus infection.

This scarlet fever study constitutes a close parallel to our own, as in each the autopsies have been performed in the same laboratory and the microscopic sections prepared by the same routine. A similar purely interstitial mononuclear infiltration was observed in

in 20 out of 89 liver sections, and in from 1 to 6 cases each in the heart, kidney, adrenal and pancreas. The 11 skin sections examined all showed slight mononuclear cell infiltration of the corium. Slight endothelial cell changes were observed in 4 of these, but in none were there the marked changes and proliferation of these cells described in measles rashes by Ewing,⁴ Mallory and Medlar,⁹ and Denton.³

The identity of the causative organism of measles does not lie within the province of this paper, but it is apparent that, in this series at least, the fatal complications of measles are due in very large part to the hemolytic streptococcus. This is evidenced by the bacteriologic studies described here, and also by the occurrence of the interstitial mononuclear infiltration and the correlation between this process and the observations cited in cases of scarlet fever, a known streptococcus disease. The large percentage of positive blood cultures at autopsy suggests that the blood stream is probably the chief route by which the organism is transmitted through the body, and the pharynx, tonsils and upper respiratory tract would seem a very likely portal of entry. This hypothesis is supported by the section of tonsil in which a blood-vessel passing through an area of acute inflammation underwent necrosis, with cocci seen passing from the inflammatory areas into the vessel.

Summary. 1. A series of 100 measles autopsies is presented, with gross and microscopic pathologic findings throughout the body, bacteriology, and various related clinical statistical data.

2. The incidence was greatest among small children, 60% of the cases falling between the ages of 6 and 24 months.

3. Pneumonia, laryngitis and encephalitis were early complications, while empyema occurred late in the disease. Death was usually in the second or third week.

4. Autopsy bacteriology studies showed hemolytic streptococcus, either alone or in combination with other bacteria, to be overwhelmingly the chief organism found.

5. No lesion definitely pathognomonic of measles was found. The most constant microscopic finding was an interstitial mononuclear cell infiltration, resembling a similar infiltrative process found extensively in scarlet fever.

In closing, I wish to express my appreciation and indebtedness to Dr. Vera B. Dolgopol, pathologist of Willard Parker Hospital, for her many helpful suggestions on the interpretation of findings.

REFERENCES.

- (1.) Brody, H., and Smith, L. W.: *Am. J. Path.*, 12, 373, 1936.
- (2.) Davidsohn, I., and Mora, J. M.: *Arch. Path.*, 14, 757, 1932.
- (3.) Denton, J.: *Am. J. Med. Sci.*, 169, 531, 1925.
- (4.) Ewing, J.: *J. Infect. Dis.*, 6, 1, 1909.
- (5.) Ferraro, A., and Scheffer, I. H.: *Arch. Neurol. and Psychiat.*, 27, 1209, 1932 (Case 1).
- (6.) Hathaway, B. M.: *Arch. Path.*, 19, 819, 1935.
- (7.) Herzberg, M.: *J. Am. Med. Assn.*, 98, 139, 1932.
- (8.) Kohn, J. L., and Koiransky, H.: *Am. J. Dis. Child.*, 46, 40, 1933.
- (9.) Mallory, F. B., and Medlar, E. M.: *J. Med. Res.*, 41, 327, 1920.
- (10.) Smith, L. W.: *Am. J. Dis. Child.*, 42, 1417, 1931.
- (11.) Warthin, A. S.: *Arch. Path.*, 11, 864, 1931.

CONGENITAL POLYCYSTIC KIDNEY.

WITH REPORT OF ITS OCCURRENCE IN SEVERAL MEMBERS
OF ONE FAMILY.

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HEREDITARY diseases, in most instances, offer certain stigma whereby they may be easily recognized. This is aptly illustrated in such hereditary afflictions as diabetes insipidus, hemophilia and others. On the other hand, in congenital polycystic kidney, it is often difficult to demonstrate any existing hereditary influence. It is by no means common, being found at postmortem in approximately 1 to 500 cases, and as such merits more than a passing interest.

This condition should be defined in contrast to other cystic conditions of the kidney, although the distinctions are not clear cut. A kidney in which there is a very great number of small cysts and larger cysts found throughout its parenchyma and projecting on its surface, both the cortex and the medulla being involved, is probably of congenital origin. The disease is not limited to any particular age, being found in fetuses, newborn, adults and even in old age. One often sees the statement in medical literature that polycystic kidney disease occurs in two periods of life, *viz.* early infancy and adult life, and furthermore, that there is a gap between these ages in which few cases occur. However, a search of the literature shows that a number of cases have been recorded occurring during the first and second decades. Sieber,⁸ in 1901, collected 32 cases in these periods; the age recorded usually represented the time when the disease was first recognized, either clinically or postmortem. Several writers, studying families with hereditary polycystic kidney disease, have recognized cases in which no subjective symptoms have developed. Such facts bring the newborn and adult groups closer together; there is no longer any doubt that the disease in the adult and the infant are the same.

Theories of Development. Many theories have been advanced to explain the development of polycystic kidney disease and presented in far more detail than could be attempted in this paper. The most generally accepted theories are:

1. That of Hildebrandt,⁶ who believes that the cysts are the outcome of a developmental defect, rather than inflammatory or neoplastic in character. The cysts, according to him, are formed as

a result of non-union of the collecting and secretory elements which arise from two separate anlagen.

2. That of Kampmeier,⁶ who, as a result of extensive embryologic studies of congenital renal cysts, comes to the conclusion that during fetal life renal cystic tabules are very common, and as growth progresses, they disappear. However, if for some unknown reason they persist and continue to grow, polycystic kidneys result.

Heredity. The hereditary aspect has been widely commented upon. Examples occurring in families cannot be regarded as a coincidence, but only as proof that in these families, polycystic kidney disease is a hereditary affection. A familial history, therefore, is of the greatest diagnostic value. This recognition of several instances occurring in one family and in several successive generations is largely responsible for the term "congenital" now used with respect to this disease. The hereditary factor is not sex-linked; the disease affects either sex equally.

Dunger,³ in 1904, was able to present 5 children of the same mother having polycystic kidney disease. Paus,⁷ in 1914, found 2 of a family of 4 with cystic kidneys; 1 of those with cystic kidney had 14 children, of whom 4 had cystic kidneys. The other with cystic kidney had 3 children, none having the disease. One of the normal members of the first generation had 4 normal children, but a grandchild had a cystic kidney. Of more recent years, Cairns,¹ noted 10 cases in 3 generations of a family. Fuller,⁴ in 1929, described 9 cases in 27 members of a family in 4 generations. While the application of Mendel's law to this condition has been suggested in the genealogic graphs published by authors, such as Cairns,¹ Crawford² and Fuller,⁴ there is still insufficient data available to admit analysis along these lines.

The cases to be reported here are those of the T. family. Medically speaking, we can start the history of this family with 2 brothers, Mendel and Isaac T. A noteworthy incident from the outset is that the parents of the children in whom the disease was found are related, that is, the husband, Isaac T. and his wife, Bessie T., are also uncle and niece. Isaac T. died at the age of 42 of "chronic nephritis." We can find no evidence of any studies, either functional or urographic having been done on him.

Bessie T., the mother, has been suffering from renal disease for a number of years and has, on several occasions, passed renal sand. Recent urologic studies reveal impaired renal function, but no evidence of polycystic kidney disease.

Bessie and Isaac T. had 7 children. Of these, 6 give positive evidence of renal disease. Four of these 6 cases have both clinical and radiologic evidence of polycystic kidney disease.

Case Reports. CASE 1.—Rose C., née T., aged 43, was admitted to this hospital on June 29, 1935, with the chief complaints of palpitation, nervousness and dyspnea, of 3 years' duration. Her past history is important in

that she suffered from nocturia for a number of years and was told that she had hypertension by a private physician. She passed a ureteral calculus in 1928.

Physical Examination. A fairly well nourished female with the following positive findings: Diseased tonsils; marked pulsations of vessels of the neck; soft systolic murmur at the mitral area not transmitted; in the upper left quadrant there was palpable a hard, rounded, pear-shaped mass which did not definitely move with respiration; the right kidney was palpable; there was a fine tremor of the fingers.

FAMILY TREE

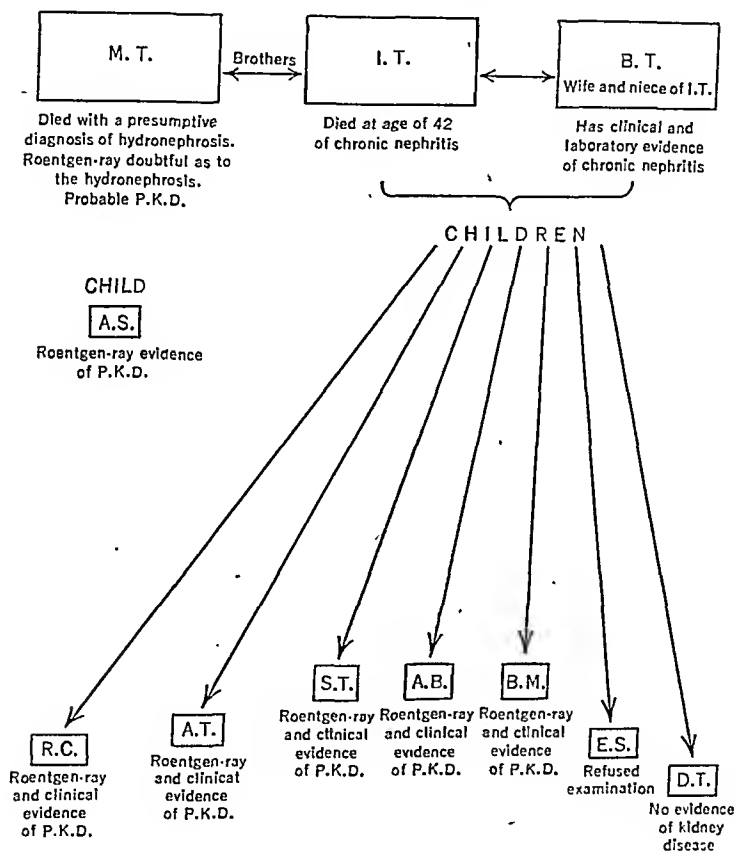


CHART I

Laboratory Studies. Temperature, 98.4; pulse, 80 to 95; respiration, 20. Urine, straw colored, acid, specific gravity, 1.016; faint trace of albumin, 2 to 3 leukocytes, occasional red blood cells, hyaline and coarsely granular cysts. *Leukocytes.* 11,400. *Urea-nitrogen,* 15.5; *Sugar,* 94; *Cholesterol,* 224. *Mosenthal Test:* impaired kidney function. *Electrocardiogram:* myocardial degeneration. *B.M.R.,* +35, +51, +28. *Urography:* Roentgen ray of right kidney showed marked dilatation of the renal pelvis; left kidney enormous dilatation of all calices. Administration of Lugol's solution caused swelling of the thyroid gland and no improvement of symptoms.

Therefore, it was not thought that this patient suffered from primary hyperthyroidism.

Diagnosis. 1, bilateral polyeystic kidneys; 2, hypertensive cardiovascular disease with hypermetabolism; 3, foci of infection. Patient discharged on July 19, 1935.

CASE 2.—Herman T., aged 36, was admitted on December 6, 1935, with chief complaints of pain in the left loin, and hematuria.

History of Past Illness. Two weeks prior to admission, patient began to develop sharp non-radiating pain in the left loin. He also noticed that his urine was reddish in color, having been so for the past 6 months. There were no other urinary symptoms, and the patient was in general good health. There was a past history of scarlet fever.

Physical Examination. A well-nourished intelligent white male. The positive findings were injected pharynx; diseased tonsils; a mass on the left side of the abdomen, in the region of the kidney, which moved with respirations. There was no tenderness nor rigidity.

Laboratory Studies. Temperature, normal. Pulse, 80; respiration, 20. Urine, amber, acid, cloudy, specific gravity, 1.011; faint trace of protein, 22 to 25 leukocytes, blood, occasional casts. Blood, mild leukocytosis, 10,900. Blood-chemistry, normal. Wassermann test, negative. Indigo carmine, right appeared in 8 minutes; left in 9. Roentgen ray, retrograde pyelogram revealed the pelvices markedly dilated and distended. There were stone shadows on the left side.

Diagnosis. Congenital polycystic kidneys with stones.

CASE 3.—Samuel T., aged 35, was admitted to the hospital on December 19, 1935, with the chief complaints of dyspnea and expectoration. He presented a history of marked asthmatic attacks of 20 years' duration.

Past History. Marked myopia since childhood. Hematuria and loin pain of 1 week's duration in 1934. At present he occasionally suffers from attacks of loin pain, frequency of urination and nocturia.

Physical Examination. Revealed dyspnea; cyanosis of lips; curvature of finger nails; marked myopia; impaired percussion at both bases; bronchovesicular breath sounds in same area; sibilant sonorous râles heard throughout, and subcrepitant râles in the bases. The heart was negative. The abdomen showed diastasis reeti, tenderness in the right loin space, and a palpable right kidney.

Laboratory Studies. Urine, straw colored, cloudy, specific gravity, 1.020, faint trace of protein, 1 to 2 leukocytes, frank blood, occasional hyaline and granular casts. Cystoscopic urine, right kidney, 10 to 60 red blood cells, occasional leukocytes, acid, cloudy. Left kidney, 5 to 8 red blood cells, occasional leukocytes. Indigo carmine, right appeared in 4 minutes; left, in 10. Blood count, normal. Roentgen-ray, retrograde pyelography revealed both kidneys larger than normal. The calices clubbed, dilated, and the upper ones enlarged.

Diagnosis. 1, Polycystic kidney; 2, bronchitis with bronchiectasis; 3, marked myopia.

CASE 4.—Anna B., née T., aged 35, has complained of fatigue and a dull pain in the lumbar region for the past 8 months. She has no urinary complaints.

Physical Examination. A slightly obese female with the following positive findings: Diseased tonsils; slight cardiac enlargement in the region of the left ventricle; a faint systolic murmur; accentuated second aortic sound; blood pressure, 160/98; fullness in the right upper and mid-abdominal quadrants.

Laboratory Studies. Urine, negative except for a faint trace of protein. Specific gravity, 1.018. Intravenous urography, revealed extensive bilateral polycystic kidneys.

Diagnosis. 1, Bilateral polyeystic kidney disease; 2, foci of infection.

CASE 5.—Belle M., née T., was admitted to another hospital in 1929 for study because of recurrent right loin pain, frequency and nocturia.

Physical Examination. Negative except for palpable lower lobe of left kidney, and marked enlargement of right kidney.

Laboratory Studies. *Catheterized urine*, revealed pus. *Indigo carmine*, right appeared in 5 minutes; left, in 6. *Roentgen ray*, pelvis and calices of both kidneys were enlarged. Marked deformity of the right kidney.

Diagnosis. Probable right-sided pyonephrosis. In 1930, the patient was admitted to the Atlantic City Hospital in a coma. She died within 2 hours, and a diagnosis of uremia with chronic nephritis was made. The original Roentgen ray plates have been destroyed, but this patient undoubtedly was suffering from the same affliction as other members of her family, with a superimposed pyogenic infection on the right side.

CASE 6.—Edith S., née T., is at the present time being treated by her family physician for kidney disease. A flat plate of the abdomen was taken 2 years ago and was found to be negative. She refused to permit further urologic studies to determine the presence or absence of polycystic kidney disease.

CASE 7.—David T., aged 25, is apparently free of renal disease. He presents no urinary symptoms nor signs, and there is no Roentgen ray evidence of diseased kidneys.

CASE 8.—Mendel, the brother of Isaac, first presented symptoms of renal disease in 1909 when he visited a physician because of recurrent attacks of hematuria and loin pain. This continued intermittently until 1919 when both kidneys became definitely palpable upon manual examination. In 1921, urographic studies revealed an irregular abnormal shadow in the left kidney region extending down to the crest of the ilium. The roentgenologist was unable to make a definite diagnosis. His interpretation was that it might either be due to a tuberculous kidney or a hypernephroma. Mendel T. continued to have hematuria, oliguria, and passage of sand, and died in 1924 with a presumptive diagnosis of hydronephrosis. In the light of the family history, it is fair to assume that Mendel also suffered from polycystic kidney disease.

CASE 9.—Mrs. S., a daughter of Mendel T., was recently in the hospital with complaints referable to the renal system. Roentgen ray evidence revealed beginning kidney lesions, viz., dilatation of calices and pelvis.

Clinical Course and Diagnosis. The majority of symptoms in polycystic kidney disease are due to renal insufficiency, a definite impairment of function being demonstrable in about two-fifths of the patients when they first consult a physician. In a typical case one obtains symptoms and signs of loin pain, hematuria, nocturia, frequency, loss of weight, unilateral or bilateral masses in the loin, hypertension, a systolic pressure of 150 mg. Hg. or higher being found in 50% of the adults with clinical symptoms, and the percentage with hypertension is still higher in the group with marked renal insufficiency. The persistent presence of hypertension in these cases is attributed to a generalized vascular disturbance as shown by the high incidence of renal sclerosis, and to the finding of obliterative changes in the arterioles and small arteries of the kidney. Whether the vascular sclerosis, especially in the kidney, is the primary factor, and the hypertension and renal functional disturbances secondary, is a moot point. The functional disturbances are similar to those found in patients with contracted kidneys. There is decreased

elimination of phenolsulphonaphthalein, retention of nitrogenous substances in the blood, and a decreased ability to concentrate the urine. Death is usually due primarily to renal insufficiency unless one of the kidneys becomes infected.

While postmortem examinations show that in many instances the polycystic kidney is not suspected in life, death being due to other causes, there are certain diagnostic and investigative procedures which serve to prove the presence of the disease.

The two most important aids to diagnosis are: a family history and the pyelogram. Very often, this latter study is the one means of making a differential diagnosis from such conditions as hydro-nephrosis and neoplastic lesions of the kidney.

Treatment. Almost all who have studied this condition are in accord with the statement that conservatism in treatment is the method of choice. Surgery carries a high mortality. The same medical treatment as is given to any nephropathy, irrespective of its cause, is used. Where infection complicates the picture, drainage and pelvic lavage often help.

Summary. 1. Polycystic kidneys in 9 members of one family are reported. 2. The importance of a careful family history and pyelographic examination as the two most important factors for such a diagnosis are stressed.

REFERENCES.

- (1.) Cairns, H. W. B.: Quart. J. Med., 18, 359, 1924-1925. (2.) Crawford, R. H.: Surg., Gynec. and Obst., 36, 183, 1923. (3.) Dunger, R.: Zur Lehre von der Cysten-niere, Beitr. z. path. Anat. u. z. allg. Path., 35, 445, 1904. (4.) Fuller, C. J.: Quart. J. Med., 22, 567, 1929. (5.) Hildebrandt: Arch. f. klin. Chir., 48, 343, 1894. (6.) Kampmeier, O. E.: Surg., Gynec. and Obst., 36, 208, 1923. (7.) Paus, N.: Deutsch. Ztschr. f. Chir., 130, 628, 1914. (8.) Sieber, F.: Ibid., 79, 406, 1905.

BOOK REVIEWS AND NOTICES.

A WOMAN SURGEON. THE LIFE AND WORK OF ROSALIE SLAUGHTER MORTON. Foreword by DR. HUGH HAMPTON of Johns Hopkins. Pp. 399; 1 illustration. New York: Frederick A. Stokes Company, 1937. Price, \$3.00.

HERE is a story to encourage the faint-hearted and to justify the superiority complex that is coupled with a compelling desire to work helpfully. Overcoming the handicaps of poverty and the family and the public opposition of the 90's to a woman in medicine, this buoyant young lady, before she was 25, had graduated from the Women's Medical College of Philadelphia, completed an internship, studied at Göttingen and Vienna (securing special favors from the leading teachers), visited Russia with the Ehrlichs, penetrated to Tolstoi's friendship, broken down Ibsen's barriers and done experiments with Horsley. It was unnecessary for her to tell us that her philosophy of life was one of action. What matter that the by-gone German words are often misspelled, and that all turns out for the best in these gilded pages? One who founded the American Women's Hospitals, was 9 times decorated for distinguished war service and who aided 60 Serbian students to an American education, can well be pardoned some poetic license when it comes to attributing all "crossness" to ill-health or announcing that the electrochemical changes of toxemia and "a chain of other pathologies" are now generally recognized, or maintaining that intelligent information and coöperation is all that is needed to obliterate disease from the earth.

This is an interesting story, well told. The bed light is turned off each night with regret, and few will not be eager to carry through to the end. Especially by the women of our profession will this autobiography be cherished.

E. K.

THE FUNDAMENTALS OF ELECTROCARDIOGRAPHIC INTERPRETATION. By J. BAILEY CARTER, M.D., Clinical Instructor, Department of Medicine, Rush Medical College, the University of Chicago; Associate Staff, Cook County and Augustana Hospitals, Chicago. With a Foreword by HORATIO BURT WILLIAMS, M.D., Dalton Professor of Physiology, College of Physicians and Surgeons, Columbia University, New York. Pp. 326; 250 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price, \$4.50.

To the number of good, concise, accurate books on electrocardiography and its clinical interpretation can now be added this. It not only has the advantage of being the latest in a still rapidly changing field, but has certain special features of advantage: an 8-page glossary for those not experienced in the specialty, and 75 pages of a bibliography of the literature of the past 20 years (classified in an alphabetical list of subjects such as acids, aconite, action currents, etc.) for those who wish to delve further. The illustrations are good and numerous, and a proper emphasis has been placed on the limitations of the method.

E. K.

AN INTRODUCTION TO COMPARATIVE BIOCHEMISTRY. By ERNEST BALDWIN, B.A., PH.D., Fellow of St. John's College, Cambridge; University Demonstrator in Biochemistry, Cambridge. With a Foreword by PROF. SIR FREDERICK GOWLAND HOPKINS, F.R.S. Pp. 112; 11 illustrations and 9 tables. New York: The Macmillan Company, 1937. Price, \$1.50.

HEREIN is presented, in a clear and logical manner, concepts of fundamental chemical adaptations, exercise of which has permitted the animal organism to function in progressively varying environments. The significance of the ionic composition of blood, which varies little from sea water and only slight variations of which are tolerated; the concept of the complex organs of man and the higher animals in terms of their biologic past, but more particularly in terms of maintenance of a stable environment against a varying external one (animal forms have resorted to semipermeable membranes and essential water-excreting mechanisms, waterproof coverings such as chitin or slime, chloride-secreting cells in the marine fish, urea-impermeable cells in marine elasmobranchs and various types of kidneys); the combat of ammonia intoxication which begins with decreased water supply; the adjustment to a non-aqueous oxygen supply by morphologic and chemical means—these are some of the problems the author presents. Morphologic and chemical data are interrelated in such a way as to give the reader information and a basis for interpretation of such study.

O. H.

HEART DISEASE. By PAUL DUDLEY WHITE, M.D., Lecturer in Medicine, Harvard Medical School; Physician to the Massachusetts General Hospital, Boston. Pp. 744; 125 illustrations. Second edition, completely rewritten and reset. New York: The Macmillan Company, 1937, Price, \$7.50.

Two valuable appendices have been added to this edition: one, giving a chronologic outline of the evolution of knowledge of heart disease; the other, a list of names recommended for cardiac diagnoses by the American Heart Association. Unfortunately, however, this is counterbalanced by a considerable reduction in the bibliography, and in that part that deals with methods of examination. Otherwise, the merits of the first edition are continued in the second.

E. K.

THE MEDICAL CLINICS OF NORTH AMERICA, VOL. 21, No. 1 (Chicago Number, January, 1937). Pp. 330; illustrated. Philadelphia: W. B. Saunders Company, 1937.

FIVE papers on Diseases of Metabolism and three on allergy contribute about one-third of this volume, the other articles being distributed over a wide range. Whether or not due to an effort to be "practical," too many of these articles exhibit an unfortunate amount of dogmatism, unproved assertion and even fallacious reasoning.

E. K.

CARCINOMA OF THE FEMALE GENITAL ORGANS. By M. C. MALINOWSKY and E. QUATER. Translated from the Russian by A. S. SCHWARTZMANN, A.B., M.D. Pp. 255; 50 illustrations (3 in colors). Boston: Bruce Humphries, Inc., 1936. Price, \$5.00.

THIS is a discussion of cancer of the female genitalia, including the breast, presented by 9 collaborators in addition to the named authors. There is a distinct emphasis on pathology and especially noteworthy is the discussion on Krukenberg tumors of the ovary, which includes original anatomic studies on the lymphatic connection between the stomach and the ovaries. The references are almost entirely from Russian and German sources and hence it is striking that no reference has been made to the use of the colpo-

scope and the Schiller test in the diagnosis of cervical cancer. The Reviewer was happy to note that Clark of Philadelphia was properly given credit for having performed the first so-called "Wertheim" operation. The omission of any mention of the rarer ovarian malignancies such as arrhenoblastoma and granulosa cell tumor is an important defect in a work of this nature, while the lack of any index and an extremely poor bibliography detracts from the value of the book.

F. B.

FAVOURITE PRESCRIPTIONS. (The Practitioner Handbooks.) Edited by SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., F.R.C.P., and ALAN A. MONCRIEFF, M.D., F.R.C.P. Pp. 227. London: Eyre & Spottiswoode, Ltd., 1936. Price, 10/6.

THIS little handbook, the first of a series of such works to be issued in conjunction with "The Practitioner," contains 18 chapters describing the pharmacopœias of 11 large general hospitals and 6 special hospitals of London, Edinburgh and Dublin and the National Formulary for National Health Insurance. There are cited numerous prescriptions which experience has shown to be valuable, and many of which have a historical interest. The Reviewer quotes a few significant sentences: "A function of a hospital pharmacopœia is to simplify the work of the dispensary and to economize in drugs and effort. To the student and young practitioner it also serves as a guide and sometimes as an inspiration;" "The newly qualified practitioner needs help in the art of prescribing, and his own hospital pharmacopœia should provide that help. . . . Surely the craftsman should know his tools and how to use them with energy and skill;" "Fashion in prescribing and in treatment is still a large factor in the choice of drugs;" "In prescribing the potent drugs, physicians tend to use less and less stock mixtures of their hospital formulary, and order instead the active principle uncombined." The physician will find here much that is interesting and useful.

R. K.

INHALATION ANESTHESIA. A Fundamental Guide. By ARTHUR E. GUEDEL, M.D., Associate Clinical Professor of Surgery (Anesthesia), University of Southern California School of Medicine. Pp. 172; 6 charts. New York: The Macmillan Company, 1937. Price, \$2.50.

THIS book has been prepared by the author with the aid of Drs. Walter Meek, Ralph Waters, Chauncey D. Leake, Peter K. Knoefel, Clinton Thienes and Douglas Drury. In the first of the two parts, there is a full discussion of inhalation anesthesia, in which the mechanism of anesthetic action, the stages and signs of anesthesia and its depths are concisely described. In addition, there is a chapter on the preparation of the patient and the selection of the anesthetic agent. The second part of the book deals with anesthetic accidents. Changes in blood pressure, ventricular fibrillation, respiratory failure, cyanosis, etc., are discussed. The last two chapters deal with the prevention of anesthetic explosions. A list of selected references is appended.

The book is an admirable one. It is prepared so that a beginner in anesthesia may easily and rapidly become acquainted with the principles of anesthetic administration. The author has stressed the physiology of anesthesia, both in the discussion of the administration of anesthesia and in pointing out the cause and prophylaxis of anesthetic accidents. Throughout the text illustrative reports of cases are inserted.

The book should be in the hands of every anesthetist and is recommended especially to beginners in the field.

L. F.

THE TRUE PHYSICIAN. The Modern "Doctor of the Old School." By WINGATE M. JOHNSON, M.D. Pp. 157. New York: The Macmillan Company, 1936. Price, \$1.75.

THERE has been considerable agitation in the past decade about the changing order in medicine; while the passing of the old-fashioned doctor has been lamented for a much longer period. One good result of this agitation has been to make it increasingly apparent that a modern type of "the doctor of the old school" has unobtrusively been emerging. The family doctor, with his trials and triumphs, professional hardships and consolations, is once more being recognized as the cornerstone of our profession. In fact, he always has been so recognized by the discerning.

This little book will tell in simple terms what the young man who is thinking of taking up medicine or the medical student or intern would like to know from one who has been through the mill. One who obviously has his fair share of the milk of human kindness not only gives out practical information of considerable value to the neophyte; but also, and more important, conveys an atmosphere of reasonable optimism that should help us all on our way toward acquiring "the true philosophy of life."

E. K.

VASCULAR DISORDERS OF THE LIMBS. Described for Practitioners and Students. By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., Physician in Charge of Department of Clinical Research, University College Hospital, London; Consulting Physician, City of London Hospital, etc. Pp. 111; 5 illustrations. New York: The Macmillan Company, 1936. Price, \$2.00.

THIS booklet may be regarded as outlining for the practitioner the results of the distinguished author's studies of the peripheral vascular diseases, somewhat as his earlier booklets on the heart followed his cardiac investigations that were so well presented in his "Mechanism of the Heart Beat." The 10 chapters cover: "The Circulation in the Limb and Its Testing;" "Effects of Circulatory Arrest;" "Embolism and Thrombosis of Main Arteries;" "Post-Ischæmic Contracture, Intermittent Claudication;" "Arteriosclerosis, Thrombo-angiitis Obliterans;" "Vasoconstriction, Local Arterial Spasms;" "Spasmodic Arterial Obstruction, Raynaud's Phenomenon;" "Gangrene (Bilateral Forms, Cervical Rib, General);" "Vasodilatation, Flushing;" "Vascular Disorders in Diseases of the Nervous System." The relatively low price makes it easy for the progressive physician to add to his medical library this authoritative statement by one who has himself added so much to our increased knowledge of disorders of the peripheral circulation.

E. K.

APPLIED DIETETICS. The Planning and Teaching of Normal and Therapeutic Diets. By FRANCES STERN, Chief of Food Clinic, The Boston Dispensary; Assistant in Medicine, Tufts College Medical School, etc. Pp. 263; many tables and charts. Baltimore: The Williams & Wilkins Company, 1936. Price, \$3.50.

EIGHTEEN years of experience in the Food Clinic of the Boston Dispensary (the first clinic of its kind in the country) in fulfilling the food prescription given by the physician, in the guidance of patients, in the instruction of students, dietitians, social service workers, nurses and physicians, furnish the background and material for this highly practical volume. Fifty-two tables simplify the computation of diets. The book is recommended to all students and physicians.

R. K.

AMINO ACID AND AMMONIA METABOLISM IN LIVER DISEASES. By **ESBEN KIRK**. Pp. 147. Copenhagen: Levin & Munksgaard, 1936. Price Dan. Kr. 10.

In his thesis for the doctorate in medicine, the author presents observations in normals and in patients with liver disease, and also experimental data on the rôle of the liver in amino acid and ammonia metabolism. It is generally agreed that the liver is the exclusive site of urea formation in the body and is also chiefly responsible for the deamination of the amino acids. The reserve of the liver in regard to both of these functions is very great, as little as one-fifth of the liver tissue being able to carry on. Thus the author failed to find any difference between normals and patients with liver disease (acute hepatitis, cirrhoses, obstructive jaundice) in the plasma amino nitrogen concentration or the amino nitrogen excretion during fasting and after glycine administration. The finding of increased blood ammonia values in liver cirrhosis is not to be explained as due to impaired urea synthesis in the liver, but, as the author shows, may be correlated with the existence in cirrhosis of a collateral circulation permitting ammonia absorbed from the intestines to avoid the liver and empty directly into the vena cava.

R. K.

CLINICAL LABORATORY DIAGNOSIS. By **SAMUEL A. LEVINSON, M.S., M.D.**, Director of Laboratories, Research and Educational Hospitals, Chicago; Associate Professor of Pathology and Bacteriology and Assistant Professor of Medicine, University of Illinois College of Medicine, and **ROBERT P. MACFATE, CH.E., M.S.**, Assistant Director of Laboratories, Research and Educational Hospitals, Chicago; Associate in Pathology and Bacteriology and Instructor of Physiological Chemistry, University of Illinois College of Medicine. Pp. 877; 144 illustrations; 13 plates (5 in colors) and 78 tables. Philadelphia: Lea & Febiger, 1937. Price, \$9.50.

"THIS book is unique among texts in its field in that it offers not only a satisfactory review of clinical laboratory diagnosis but presents special chapters on laboratory procedures in legal medicine and toxicology, in pediatrics and in similar subjects not usually included in a book of this character. It provides a rapid review of the entire field, correlating the didactic subjects with clinical diagnosis. The technique for obtaining and examining the various materials is given and the pathologic findings are compared with the normal. Brief reviews of anatomy, physiology, biochemistry and of the outstanding diseases aid the intern and the practicing physician in the study of those cases requiring laboratory methods. . . . The system of hematology and the histologic technique employed are those of Dr. R. H. Jaffé, of the Cook County Hospital in Chicago. The chapter on Pediatric Procedures is contributed by Dr. H. G. Poncher, of the University of Illinois, College of Medicine, while the technique for the toxicologic examination of materials is that formulated by Dr. C. W. Muehlberger, Coroner's Toxicologist, Cook County, Illinois." (Publisher's statement.)

NEW BOOKS.

Diagnosis and Non-operative Treatment of the Diseases of the Colon and Rectum. By **GOTTFALD SCHWARZ, M.D.**, Professor, University of Vienna; Head X-ray Department, Kaiserin Elizabeth Hospital, Vienna, and **JACQUES GOLDBERGER, M.D.**, Consulting Physician, Carlsbad, and **CHARLES CROCKER, M.D.**, New York, N. Y. Pp. 540; 246 illustrations and 9 colored plates. New York: Paul B. Hoeber, Inc., 1937. Price, \$10.50.

Autonomic Neuro-effector Systems. (Experimental Biology Monographs.) By WALTER B. CANNON, George Higginson Professor of Physiology, Harvard University, and ARTURO ROSENBLUETH, Assistant Professor of Physiology, Harvard University. Pp. 229; 42 illustrations. New York: The Macmillan Company, 1937. Price, \$4.00.

Epidemiologie. Grundbegriffe und Ergebnisse. By PROF. DR. MED. ADOLF GOTTSSTEIN, Ministerial-Direktor i. R., Berlin. Pp. 285; 16 illustrations. Wien: Franz Deuticke, 1937. Price, Paper, M. 15; Bound, M. 17.40.

Pression Solaire Faisceau Énergétique et Biologie. Biogenèse et Pathogenèse. By DOCTEUR G. FROIN, Ancien Interne des Hôpitaux de Paris. Pp. 327; 38 illustrations. Paris: Librairie Girardot et Cie, 1937. No price given.

The British Encyclopædia of Medical Practice. Volume 3. Cataract to Diaphragm Diseases. Under the General Editorship of SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge, etc. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P.; G. GREY TURNER, D.Ch., M.S., F.R.C.S.; JAMES YOUNG, D.S.O., M.D., F.R.C.S. Ed., F.C.O.G.; SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., and F.M.R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 735; 77 illustrations and 12 plates (8 in color). London: Butterworth & Co. (Publishers) Ltd., 1937. Price, \$12 per volume.

This volume covers some 60 odd articles from "Cataract" to "Diaphragm Diseases"—none of outstanding length. The reader is referred to this Journal (193, 711, 1937) for a consideration of the earlier volumes.

Personality and the Cultural Pattern. By JAMES S. PLANT, M.D., Director, Essex County Juvenile Clinic. Pp. 432. New York: The Commonwealth Fund, 1937. Price, \$2.50.

Pediatric Dietetics. By N. THOMAS SAXL, M.D., F.A.C.P., F.A.A.P., Associate and Lecturer in Diseases in Children, New York Post-Graduate Medical School, Columbia University; Assistant Attending Physician, Babies' Ward, New York Post-Graduate Hospital, etc. Foreword by ADOLPH G. DE SANCTIS, M.D., F.A.A.P., Director of Pediatrics at the New York Post-Graduate Medical School and Hospital, Columbia University. Pp. 565; 57 illustrations and 2 colored plates. Philadelphia: Lea & Febiger, 1937. Price, \$7.00.

Annual Report of the Indian Institute for Medical Research 1935-1936. Issued by the Governing Body. Pp. 84. Calcutta: Indian Institute for Medical Research, n.d.

Maternal Care. The Principles of Antepartum, Intrapartum, and Postpartum Care for the Practitioner of Obstetrics. Approved by The American Committee on Maternal Welfare, Inc., Prepared by Drs. W. C. DANFORTH, G. W. KOSMAK, R. L. DENORMANDIE, F. L. ADAIR. F. L. ADAIR, Editor. Pp. 93. Chicago: The University of Chicago Press, 1937. Price, \$1.00.

The Biology of Human Conflict. An Anatomy of Behavior, Individual and Social. By TRIANT BURROW, M.D., Ph.D., Scientific Director, The Lifwynn Foundation, New York City. Pp. 435. New York: The Macmillan Company, 1937. Price, \$3.50.

Papers from the IV Medical Service of St. Erik's Hospital, Stockholm. Edited by HILDING BERGLUND. Pp. 269; illustrated. Stockholm: Alb. Bonniers Boktryckeri, 1937.

League of Nations. Bulletin of the Health Organization. Vol. VI, No. 1 (February, 1937). Edited by Health Section of the League of Nations, Geneva. Pp. 127; 24 illustrations. New York: Columbia University Press, 1937. Price, 65c.

The Medical Clinics of North America, Vol. 21, No. 3 (Mayo Clinic Number, May, 1937). Pp. 956; illustrated. Philadelphia: W. B. Saunders Company, 1937.

This number contains 21 articles, including a symposium on gastro-intestinal diseases by A. B. Rivers and L. A. Carlson (Some Extragastric Causes of Dyspepsia); J. F. Weir (Pancreatitis); P. W. Brown (Constipation); J. A. Barger (The Treatment of Diarrhea); E. G. Wakefield ("Spastic Colitis"; Functional Disorder of the Colon Affecting Young and Middle-aged Individuals); D. L. Wilbur (Vitamin Deficiency Diseases: Their Diagnosis and Treatment).

Infantile Paralysis and Cerebral Diplegia. Methods Used for the Restoration of Function. By ELIZABETH KENNY. With a Foreword by HERBERT J. WILKINSON, Professor of Anatomy and Dean of the Faculty of Medicine, University of Queensland. Pp. 125; 51 illustrations. Australia: Angus & Robertson Limited, 1937. Price, £1/1/-.

International Clinics. Vol. II. Forty-seventh Series, 1937. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 13 Collaborators. Pp. 315; many illustrations, 1 in color. Philadelphia: J. B. Lippincott Company, 1937.

The usual wide range of subjects is covered in this volume entirely by American writers.

Twins. A Study of Heredity and Environment. By HORATIO H. NEWMAN, FRANK N. FREEMAN, KARL J. HOLZINGER. Pp. 369; 33 figures, 39 plates of illustrations and 96 tables. Chicago: The University of Chicago Press, 1937. Price, \$4.00.

NEW EDITIONS.

The Treatment of Diabetes Mellitus. By ELLIOTT P. JOSLIN, M.D. (HARVARD), M.A. (YALE), Medical Director, George F. Baker Clinic, New England Deaconess Hospital; Clinical Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital. With the Coöperation of HOWARD F. ROOT, M.D., Physician, New England Deaconess Hospital; Instructor in Medicine, Harvard Medical School, PRISCILLA WHITE, M.D., Physician, New England Deaconess Hospital; Instructor in Pediatrics, Tufts College Medical School, ALEXANDER MARBLE, M.D., Physician, New England Deaconess Hospital; Assistant in Medicine, Harvard Medical School. Pp. 707; 22 illustrations and 142 tables. Sixth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, \$7.00.

Surgical Anatomy. By GRANT MASSIE, M.B., M.S. (LOND.), F.R.C.S. (ENG.), Assistant Surgeon, Guy's Hospital; Lecturer in Operative Surgery, Guy's Hospital Medical School. Pp. 468; 153 illustrations, many in color. Third edition. Philadelphia: Lea & Febiger, 1937. Price, \$6.50.

"Since the last edition of this book appeared yet another change in anatomical nomenclature has come about, and the situation from the viewpoint of the teacher of surgery is even more confused. In these circumstances it has appeared to the author that the purpose of this book is best served by retaining the old nomenclature, giving as hitherto the B.N.A. in brackets, and by making use of such terms descriptive of position as medial and lateral, which are so obviously better. . . . The text has been carefully revised and various additions and alterations have been made. As hitherto, every effort has been made to strike a balance between the anatomical and surgical matter. The number of illustrations has also been augmented." (From author's Preface.) (For reviews of previous editions, see this Journal 176, 727, 1928; 187, 412, 1934.)

The Morphine Habit and Its Painless Treatment. By G. LAUGHTON SCOTT, M.R.C.S., B.A. (OXON.), Late Senior Physician, London Neurological Clinic; Late Chief Assistant, Neurological Department, Guy's Hospital. Pp. 105. Second edition. London: H. K. Lewis & Co., Ltd., 1937. Price, 5s.

The Alimentary Factor in Disease. By MAX. H. KUCZYNSKI, M.D., D.Sc., Pathologist to the Ministry of Public Health of Peru; Professor of Physiopathology at the University of San Marcos, Lima, Peru, etc. Pp. 130. Second edition of "Studies on Nutrition." The Hague: G. Naef, 1937. Price, 3 Guilders.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
JOHN H. MUSSER

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

SOME CLINICAL ASPECTS OF CERTAIN BACTERIAL DISEASES.

THE application of the routine use of blood cultures to patients with fever of undetermined etiology often leads to surprising results in the establishment of a diagnosis. One cannot overemphasize the importance of this procedure not only in long continued fevers but in febrile states of short duration as well. In addition to the usual cultural methods, the inclusion of an anaërobic technique is necessary to complete the worth of this diagnostic aid. The bacteroides group demonstrates the wisdom of such thoroughness.

Bacteroides Infection. Much interest has been aroused in the continental literature, particularly in France, in bacteroides and related infections. Few reports have reached the English literature, but those which have, demonstrate clearly that a more widespread recognition of these infections probably awaits an increased interest in them rather than an increased frequency of occurrence.

While described in Europe and the United States as early as the turn of the century,¹⁴ it was not until 1919 that Castellani and Chalmers⁹ brought under the term *bacteroides* the large group of non-spore-forming obligative anaërobic bacilli. Certain Gram-positive anaërobic cocci cause similar symptoms as well and must be kept in mind in a discussion of this group. While these anaërobic are specifically distinct from one another³⁴ they have in common the characteristic of living as saprophytes in the natural cavities of the human body, the mouth, pharynx, intestine and genito-urinary tract. Most important of this group clinically has been *Bacteroides funduliformis*, particularly in Parisian infections.³⁴ For an adequate consideration of the bacteriological aspects the reader is referred to the paper of Henthorne, Thompson and Beaver.²²

Thompson and Beaver⁵⁰ in 1932 found 10 reported cases due to *Bacteroides fragilis* and *Bacteroides funduliformis*. None were in the English literature. They reported 2 cases with organisms isolated from the blood by an anaërobic technique. Both patients had lesions in the genito-urinary tract, one prostatic hypertrophy, the other carcinoma of the bladder. In both these patients the disease was not a primary one, serious pathologic states being present and paving the

way for this most serious complication. Both patients developed infected pulmonary emboli with septic infarction. Cohen¹¹ has reported *Bacteroides funduliformis* in lung abscess and Beaver, Henthorne and Macy⁵ in sepsis with hepatic abscess. Dixon and Deuterman¹⁴ have more recently added 5 new cases.

Lemierre's³⁴ description of the clinical features of these septicemias is clear and complete. From the sites where these organisms live as saprophytes, that is, in the mouth, tonsils, middle ear, mastoid, appendix, puerperal uterus and urinary tract, during an inflammatory process these organisms, commonly *Bacteroides funduliformis*, find their way to the blood stream where infected emboli are released. Regardless of origin there are certain clinical characteristics common to the group, producing a syndrome "so characteristic that it permits of diagnosis before bacteriologic examination, including blood culture, has provided conclusive proof." He further points out that the postanginal septicemia, described as due to *Bacteroides funduliformis*, has the same general features as the septicemia ascribed in the older German literature to *Bacillus symbiophiles* and that *Fusobacterium nucleatum*^{18a} isolated in several cases in Zurich is identical with *Bacteroides funduliformis*. Although symptoms depend largely on the organs involved, the symptomatic triad, high fever, pulmonary infarcts, and suppurative arthritis, is commonly present. Dixon and Deuterman found the liver affected in most cases and jaundice, varying from moderate to extreme, occurred 4 to 7 days after the onset of infection. Lemierre found jaundice less constantly, but considers it highly significant when present. Septicemia in otitis media has followed suppurative thrombophlebitis of the cavernous sinus. In posttonsillitis cases, as well, venous thrombosis seems to be a link between the tonsillitis and the generalized infection.^{18b} Autopsy on such cases has shown peritonsillar thrombophlebitis and accounts for the procedure of internal jugular ligation as a therapeutic measure.

Dixon and Deuterman's 5 postoperative cases occurred in patients from 35 to 64 years of age and symptoms of bacteremia began 10 to 18 days postoperatively, interrupting an uneventful convalescence with a chill and sudden elevation of temperature, followed by daily chills and temperature to 106° F. They describe profuse perspiration as a distinctive feature. Five to 7 days may elapse following development of symptoms until blood cultures become positive.

Lemierre's³⁴ patients were mostly adolescents or young adults of either sex with either an inadequately drained tonsillar or peritonsillar abscess or deep-seated tonsillitis. In those in whom the syndrome develops 4 to 5 days following the onset of local inflammation, a true chill and high fever occur. At times the symptoms do not develop until as late as 12 days, sufficient time elapsing for the initial fever to have disappeared. Cervical adenopathy is present. All such infections seen by Lemierre have not been pure septicemias. All have been accompanied by the formation of distant metastatic abscesses, particularly in the lungs, even as early as the first day. These lesions start as septic infarcts with pain and dyspnea, and even blood stained sputum, a pleural friction rub and râles. Empyema has occurred. Joint lesions are very frequent, ranging from simple pains to suppurative arthritis, particularly in the shoulders, elbows, knees, sternoclavicular or sacro-

iliac articulations. Icterus has already been mentioned. Suppuration elsewhere may occur, for example, in the peritoneal cavity and psoas muscle. There is usually a leukocytosis and, in chronic cases, an anemia.

The course of the disease varies. Rapid and fatal termination in 7 to 15 days may occur. Such patients have continuously high fever, prostration, and die in coma. The disease may last 3 to 6 weeks with irregular fever ending in cachexia and delirium. An extremely grave prognosis accompanies the condition. Of 20 cases observed by Lemierre only 2 recovered. Dixon and Deuterman's mortality was 83 %.

Lemierre states "to anyone instructed as to the nature of these septiciemias it becomes relatively easy to make a diagnosis on the simple clinical findings. The appearance and repetition several days after the onset of a sore throat (and particularly of a tonsillar abscess) of severe pyrexial attacks with an initial rigor, or still more certainly, the occurrence of pulmonary infarcts and arthritic manifestations, constitute a syndrome so characteristic that mistake is almost impossible." Final diagnosis, of course, rests on bacteriologic ground—smears, cultures, and animal injections.

Treatment is purely supportive. No specific therapy is known. Antiseptic dyes have been used intravenously but with poor results.

Pyocyaneus Infection. Recent years have produced the recognition of a number of clinical pictures caused by commonly known organisms but not generally associated with the usual expressions of infection with these bacteria. *B. pyocyaneus* is one of these organisms. A well known pyogen, it is widely distributed in nature and usually considered a secondary invader of low virulence. Most characteristic of its growth is the production, in the presence of abundant oxygen, of a bright bluish-green fluorescence. It usually lives in saprophytic contentment in the normal mouth, skin and intestines of man; but at times takes on sufficient pathogenicity to contaminate surgical wounds and, more rarely, still greater pathogenicity to produce localized and generalized infection, not only following secondary implantation, but also as a primary invader.

Although some authorities still look with skepticism upon the possibility of generalized pyocyaneus infection, there is now sufficient evidence in the literature clearly to indicate its characteristic symptomatology as well as its reality.^{6,17,20,35,39,51} To be sure, generalized infection is uncommon and occurs most often in children and debilitated adults,¹⁷ but it may also attack the healthy mature individual.

Pyocyaneus infection is most logically divided into two types, localized and generalized, and these in turn may run acute or chronic courses.

Among the *localized* forms, the common wound infection, discharging a bluish-green pus, needs no discussion. At times the virulence may be increased to the extent that contamination leads to hospital epidemics not only in surgical wounds, but in the umbilical wound and, through contamination of feeding bottles, the enteric tract of the child, resulting in a diarrheal syndrome.¹²

In the eye, corneal involvement is most serious and follows the implantation of a foreign body. Ulcerative keratitis results, often leading to panophthalmitis.^{31,45} The clinical course is usually rapid and severe. Evisceration often becomes necessary, but occasionally cases

reach a chronic stage with favorable response to treatment. Dacrocystitis, punctate keratitis and conjunctivitis have also been reported.

Infection of the ear is of two types. In the middle ear it is usually superimposed upon an already existing otitis media. Direct extension to the mastoids and from there to the meninges and brain has been reported. In the external ear the infection appears to be primary. It may be unilateral or bilateral. Onset may be acute or insidious and there is a tendency for the process to become chronic.²³ Subjectively, the patient experiences throbbing and pain and, on examination, diffuse redness and exudation are found. With the development of chronicity, pain recedes and pruritus appears with thickening and scaling of the epithelial surface. The organism may be found in the exudate but pigmentation is not constant. Reports of vaccine therapy²³ are very enthusiastic in this type of infection.

One of the most important of the local types of pyocyaneus infection is involvement of the gastro-intestinal tract. *B. pyocyaneus* is not unusual in the ulcers of agranulocytic angina. Attempts^{29,39} to associate the organism with the etiology of this interesting disease have all met with failure, and in the light of our present knowledge of agranulocytosis such findings represent secondary invasion in spite of the work of Lovett³⁶ demonstrating a depressant effect on the white blood count in guinea-pig inoculations. Likewise, since the organism normally inhabits the gastro-intestinal tract, its recovery from specific ulcers, such as those of tuberculosis and cancer, is not surprising.

Lesions of the pharynx, esophagus, stomach and intestines occur. Diarrhea in children has already been mentioned. Such symptoms occur in adults as well, particularly in tropical regions and in association with generalized infection. Mucus and blood may appear in the stools. Greenish discoloration of the stools has also been noted.

Localized infection often spreads by contiguity and contact. Infection transferred to the exposed surfaces of the body by contact has led to confusion with pellagra.^{3,30} The development of mastoiditis and its complications have already been noted. In the upper respiratory passages, bronchitis, lung abscess, bronchopneumonia and pleurisy may follow. Endometritis may follow puerperal infection and in the urinary tract, ascent to the kidneys has resulted from cystitis.

Generalized infection with *B. pyocyaneus* is rare. Fraenkel¹⁹ found only 13 primary cases in 12,000 autopsies. Such infections start from a localized lesion, often in the middle ear or colon. The source may not be known and the infection appear generalized from the onset. A description of the clinical picture is worthy of repetition. Onset is usually sudden in the acute type with symptoms which resemble closely those of other types of septicemia. Gastroenteric symptoms such as nausea, vomiting, and diarrhea, together with cough and dyspnea are the rule. The temperature is high and of the septic type. Generalized pains, in the head, back and extremities develop. The spleen may be palpable. An eruption appears, most commonly maculopapular and red to blue in color. These lesions develop rapidly and fade slowly. Recurrent crops have been noted. Other types of lesion seen are hemorrhagic or ecchymatous, and eruptions resembling erythema multiforme or erythema nodosum. It is clear that confusion with typhoid fever may and has easily occurred in such patients.

The fever known as "13-day fever" or "Shanghai fever" has been traced to *B. pyocyaneus*.³⁵ The skin eruption, together with splenic enlargement and a febrile course ending by lysis in 2 to 3 weeks, closely resembled typhoid fever, but the occurrence of leukocytosis, the isolation of *B. pyocyaneus* from the blood and excretions together with agglutination reactions as high as 1 to 400 clearly established the diagnosis.

Chronic generalized infection may follow the acute stages, but more often it begins insidiously without the acute pictures described above.⁸ Freeman's case is an excellent example,²⁰ as shown by the long course, irregular septic fever, chills and sweats, a cutaneous eruption, neuralgic pains, especially in the extremities, and paresis and muscle atrophy of the legs. The latter symptoms, paresis and muscular atrophy, are apparently due to the exotoxin which is said in animal experimentation to produce paralysis and wasting. Great emaciation and weakness are also seen in chronic infection, and anemia usually develops.

In such a septicemia, metastatic lesions often develop, involving almost any organ, including those already mentioned in localized infection as well as the liver, gall bladder, spleen, the heart, serous cavities and joints.

Meningitis has already been mentioned as a complication of mastoiditis. Cases⁴¹ have also been reported following infection of the nasopharynx and orbital cellular tissue. Reports are also available describing meningitis following generalized infection, traumata of the brain or spine, and in 1 case, so-called "primary" infection without known portal of entry.⁵¹ Development following spinal puncture⁴⁶ is also well known. Symptoms and signs are those of meningococcal meningitis, and need no repetition here. At times symptoms have shown an exacerbation following diagnostic spinal puncture.

Encephalitis ascribed to pyocyaneus toxin in the absence of organisms in the brain³² has been reported.

Diagnosis of pyocyaneus infection in draining wounds usually follows recognition of characteristic pigmentation of the pus or dressings. Pigmentary change cannot be relied upon, however, because of the lack of its production when the oxygen supply is inadequate. This may happen even with superficial infections, for example in the external ear. Diagnosis must rest, therefore, upon the demonstration of the organism in causative relationship to the lesion,⁴⁷ a difficult problem in the gastro-intestinal tract.

In generalized infection the clinical picture is not diagnostic. At times the characteristic skin lesions with gastroenteric symptoms and paresis of leg muscles leading to atrophy may be suggestive, but again the clinical picture may not be typical. Positive blood culture is conclusive, but is not always obtainable especially in the chronic stage. In Freeman's case²⁰ bile cultures at operation were successful when blood cultures were negative.

Prognosis in localized infection is invariably good, except in involvement of the eye. In generalized infection, prognosis varies from excellent in transient bacteremia⁴⁷ to very poor in sudden and severe infections. Recovery is not unusual in chronic generalized infection and in meningitis.

Meningococcemia. The common clinical picture of meningitis with headache, vomiting, fever, eruption, stiff neck, focal neurologic signs and

a positive spinal fluid comes to mind when the meningococcus is mentioned, but the occurrence of meningococcal disease without meningeal involvement is not sufficiently well known. This is all the more surprising when one realizes that 35 years have elapsed since Salomon⁴³ first reported a case of chronic meningococcemia. Up to January, 1931, Binns and Fothergill⁷ were able to find only 19 reported cases in the American literature and over 100 cases in the foreign literature. Such figures can only indicate a lack either of recognition or of recording of such cases, particularly in this country. An increasing number of reported cases since that time supports the supposition that increased recognition of this clinical picture awaits the education of the American physician to the possibility of its presence in febrile disorders. This is particularly important since the clinical picture is sufficiently characteristic to permit a tentative diagnosis before blood culture confirmation is obtained.

Orientation as to the place of both acute and chronic meningococcemia in meningococcus infections may be gained from a brief consideration of the pathogenesis of cerebrospinal fever. There is general agreement that the meningococcus first finds its way into the upper respiratory passages, where it may or may not call forth an inflammatory reaction. From this point on, the theories of infection become divergent. Among them we find the theory of direct extension, which postulates a direct spread to the meninges, for example, by way of the sphenoid or ethmoid lymphatics or by the olfactory nerve. Another group believes that septicemia first develops following upper respiratory infection with hematogenous spread to the meninges. This mechanism is championed by Herrick,^{24a,b,c} who, during the World War, demonstrated positive blood cultures preceding infection of the spinal fluid. He divides infection into 3 stages: first, a carrier stage or infectious stage in the upper air passages, usually of short duration leading to a second stage of bacteremia, which, in a short time, usually within 48 hours, is followed by a metastatic phase, in which the meninges are involved in about 90 % of the cases. The latter is the stage with which most of us are familiar and may occur sufficiently early to appear as the initial process. While one cannot doubt the possibility of infection of the meninges by direct extension, evidence is adequate to state that in many cases meningeal involvement is secondary to bacteremia.

The observations of Herrick have led Graves, Dulancy and Michelson²¹ to classify meningococcemia into two types; first *acute meningococcemia*, of less than a week's duration before localization in the meninges occurs. Into such a group fall those patients with fulminating meningococcemia of sudden onset with marked sepsis, a petechial eruption, a clear cerebrospinal fluid and death within 8 to 24 hours following the initial chill. Such patients are usually in good health and suddenly develop symptoms of overwhelming infection leading to death before signs of meningitis appear. Restlessness, vomiting and abdominal pain quickly develop. Prostration is marked. The temperature varies from high to subnormal values. Stupor is common. Cyanosis or a mottled pallor may develop and a petechial rash makes its appearance, often with great suddenness and especially over the extremities, buttocks and back. In several days these lesions may fade leaving a brown stain. Such a picture is sometimes described as the

Waterhouse-Friderichsen syndrome.¹ Grossly, postmortem evidence of meningitis in such patients is absent or slight.

When bacteremia does not lead to such fulminating infection, the usual text-book picture of meningococcal meningitis generally develops.

The second group in the classification of Graves and his associates is *subacute or chronic meningococcemia*, in which the bacteremia persists more than a week before localization occurs, if it does so at all. Into this group falls the second class of cases now under discussion, meningococcemia with metastatic spread to the joints, heart (endocardium), pleura, conjunctiva and, finally, at times, to the meninges, as well as meningococcemia without evidence of metastatic infection at all.

Chronic meningococcemia displays a clinical picture so characteristic that, if one has the possibility in mind, diagnosis may be made at the bedside. Laboratory confirmation is, of course, necessary. This symptom complex may occur at any age. Ninety per cent of the cases, however, have been found in the third and fourth decades.⁴² In an analysis of 68 cases, Dock¹⁵ found only 10 females. However, 41 of the reported patients were soldiers. In civilian practice² sex distribution is about equal.

Onset is usually described as sudden^{24a} with headache, fever, and chills or chilly sensations. More rarely the onset is insidious, and Stewart-Wallace states it is usually so, with malaise and pain in the limbs. Evidence of upper respiratory-tract infection may be present or absent. A triad of symptoms, intermittent chills and fever, arthralgia, and a skin eruption, makes up the essential features of the disease.

Fever is often remittent and may rise to 104° or more. At times, intervals as long as 10 days may separate the febrile periods.² The febrile episodes of all types of malaria may be closely imitated. Dock, in the 68 patients mentioned above, found intermittent fever daily in 49, 2-day cycles repeatedly in 37, 3-day cycles in 21, and 4-day cycles occasionally in 3. Chills or chilly sensations often accompany the recurring bouts of fever.

The eruption may vary in nature, size and distribution. It usually makes its appearance in the first week. Rarely, it may be absent. The extremities are the most frequent site, but it also occurs on the chest and face and, less commonly, on the abdomen and back. The lesions are usually maculopapular and rose red in color but may vary from faint pink to deep red. Size varies from that of a pinhead to several centimeters in diameter. Disappearance time varies from 36 hours⁷ to 7 days⁴⁸ and the remaining stain which has been described as brown to bluish-red gradually fades. New lesions often appear with recurring fever. Erythema multiforme and erythema nodosum may be simulated. Tenderness is sometimes present. Petechiæ are common and do not disappear on pressure. Pustules have been described.² Biopsy of lesions from one of Stewart-Wallace's cases disclosed no specific microscopic pathologic changes.

Arthralgia may be a striking feature of the disease. Such pains are usually migratory without evidence of inflammation in the joints. Swelling and tenderness may occur, however, but suppuration of the joints is uncommon.

Physically, these patients may show a paradox of severe sepsis and an apparently good general condition⁴⁰ especially between bouts of

fever. The eruption and fever may be the only positive physical signs, although at times the spleen may be palpated.

Differential diagnosis may be difficult. This is especially true with subacute bacterial endocarditis, particularly since endocardial metastases resulting in bacterial endocarditis may be a part of the disease itself. The occurrence in both diseases of embolic phenomena in the skin, kidneys and spleen, the septic course, joint pains without local inflammation, and positive blood cultures⁴⁰ demonstrate their similarity. Typhoid fever, brucellosis, malaria, rheumatic fever, miliary tuberculosis, gonococcal sepsis, erythema multiforme and erythema nodosum are also confusing.

Although our particular interest lies in those patients having had no meningitis until, perhaps, the terminal stages of the disease, such a picture may develop following meningitis.³³ The clinical picture is not peculiar to any one type of meningococcus.⁴⁸

The course of the disease varies from several weeks to many months and prognosis is, in general, good. Complete recovery has taken place in 75 to 90% of reported cases.^{7,48} In fatal cases, endocarditis or terminal meningitis are common, particularly the former, but recovery has often been reported with both of these complications and their exact status in prognosis is not yet clear. Other complications worthy of mention¹⁵ are anemia, empyema, suppurative orchitis, interstitial nephritis, thyroiditis, prostatitis, retinal hemorrhage, iridocyclitis, and extradural abscess.

Final diagnosis rests upon positive blood culture. At times there may be difficulty in the isolation of the organism and negative cultures do not rule out the disease. Enriched media are essential for good results. McLean and Caffey³⁸ have pointed out the value of smears from the purpuric spots as an aid in the early diagnosis of meningococcal bacteremia. Smears are made from the material obtained by stab wound from the purpuric area and stained for Gram-negative intracellular diplococci. In 18 cases examined by them 15 (83%) were positive. Such a procedure is not a substitute for a blood culture but may lead to a tentative identification of the organism 12 to 72 hours before cultures are available for analysis. Agglutination reactions are, in general unsatisfactory. There appears from recent reports² to be no contraindication to the use of diagnostic spinal tap in the absence of meningitic signs.

Treatment is not to be considered here. Adequate discussions may be found in the more recent literature.^{2,7}

Enterotoxic Staphylococcal Food Poisoning. Food infection of the type characterized by gastro-intestinal symptoms, nausea, vomiting, abdominal cramps, and diarrhea with varying degrees of prostration, which occurs in epidemics, persists for 24 to 48 hours and entails an extremely low mortality has invariably been associated with the salmonella group of organisms. More recently, however, the increasing number of such outbreaks ascribed to staphylococci has created considerable interest in the potentialities of this organism in the production of such symptoms. The bacteriologic aspects of the staphylococci have recently been reviewed in these columns²⁵ but little was said at that time concerning clinical and epidemiologic problems of food poisoning. In this disease, like many others of recent general recognition, first

description goes back many years. Barber⁴ in 1914 noted the occurrence of the usual symptoms of food poisoning in himself and other individuals visiting a certain farm in the Philippines. He traced the cause to milk infected with staphylococci and noted further that fresh milk was harmless, and that its effectiveness in the production of symptoms developed only after standing some hours at room temperature. He also described the short incubation period of approximately 3 hours which has characterized subsequent outbreaks reported by others.

Despite Barber's early report, interest in, and recognition of, the staphylococcus as a cause of food poisoning has become general only in the past 6 years. Further reports of milk infection^{13,44,49} have appeared, but the chief offending foods have been baked goods, particularly those with cream fillings.^{26,37} Cheese and gravies have also been responsible.²⁸ In all, the symptomatology has been uniform. The incubation periods have been short. Approximately 3 hours after the ingestion of contaminated food, nausea, vomiting, and diarrhea make their appearance. In salmonella infection, the incubation period is often longer with a meal intervening between the intake of infected food and the development of symptoms.

The shortness of the incubation period suggests the ingestion of a toxin rather than the development of infection within the patient. The report of Barber also suggests a toxin in that fresh milk was harmless unless it stood several hours before ingestion. Numerous investigations on volunteers have confirmed these suspicions, in that the ingestion of sterile filtrates of the isolated organisms has in many instances duplicated the symptoms in their entirety.

The modes of contamination of milk are many. In Barber's original description⁴ and in several outbreaks in the United States^{13,44} mastitis of a recurrent type, garget, was demonstrable. Crabtree and Litterer¹³ found, in two cows supplying milk to the group under observation, udders with pus pockets periodically releasing large numbers of staphylococci. In Tanner and Ramsey's report,⁴⁹ intentionally contaminated milk was ingested for experimental purposes. Ice cream made from contaminated milk has also caused symptoms.⁴⁴

The sources of contamination in outbreaks due to baked goods are not as evident. Presumably contaminated ingredients or the introduction of infection during the preparation of foods might occur. Jordan and Burrows²⁶ were unable to find staphylococci in significant numbers in the ingredients used in the production of known contaminated baked goods. Milk was not examined. Batter prepared by 7 different men in one of the implicated bakeries disclosed similar results. However, during the process of preparation, especially of cream-filled pastries, abundant opportunity for contamination with staphylococci exists. Since Jordan, Dack and Woolpert²⁷ have shown that the product of the bacteria responsible for symptoms may resist boiling for 30 minutes, one must bear in mind, as the source, ingredients containing the enterotoxin before exposure to heat. Baked goods are likely to be kept at temperatures quite favorable to the multiplication of any bacteria present.

The recognition of a particular type of staphylococcus responsible for such symptoms would be an exceedingly valuable contribution to both diagnosis and prevention. Jordan and Burrows²⁶ have carried

out studies to settle these problems. They have definitely established the fact that there are no characteristic bio-chemical or serologic reactions. Staphylococci of diverse origin and different cultural and agglutinative characteristics may elaborate a substance which is toxic on ingestion. They also found that strains from normal throats, from human septicemia, osteomyelitis and local abscess may produce a substance which induces vomiting in human volunteers. These organisms were either *S. aureus* or *albus* and differed in speed and type of gelatin liquefaction and in the degree of hemolysin production. Partial confirmation of these results has been reported by Chinn.¹⁰

The ubiquity of the staphylococcus and the infrequency of outbreaks of food poisoning caused by it suggest that either this cause of food poisoning is often unrecognized or unusual strains of the organism and exceptional environmental circumstances are necessary for the production of the enterotoxin.¹⁶ Dolman, in a series of procedures designed to support the latter views, demonstrated the independence of the exotoxin and the food poisoning substance. His results indicate that the enterotoxic substance, the nature of which is still obscure, is probably produced by only a few strains of staphylococci, as a special metabolite, the formation and excretion of which are favored by a semifluid medium and an atmosphere high in carbon dioxide. Although he states that it is difficult to imagine such circumstances in contaminated foodstuffs, baked goods, particularly of the cream-filled variety, appear to this Reviewer to be an ideal site. They are semisolid, but the carbon dioxide content, under these circumstances, is an open question. Definite establishment of Dolman's views would explain the infrequency of staphylococcal food poisoning in the face of the universal distribution of this organism.

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REFERENCES.

- (1.) Aegerter, E. E.: J. Am. Med. Assn., 106, 1715, 1936. (2.) Applebaum, E.: AM. J. MED. SCI., 193, 96, 1937. (3.) Ashby, W. M., Eldridge, W. W., and Freeman, W.: J. Am. Med. Assn., 88, 1307, 1927. (4.) Barber, M. A.: Philippine J. Sci., 9, Sec. B, 515, 1914. (5.) Beaver, D. C., Henthorne, J. C., and Macy, J. W.: Arch. Path., 17, 493, 1934. (6.) Bhatnagar, S. S.: J. Roy. Army Med. Corps, 63, 331, 1934. (7.) Binns, J. F., and Fothergill, L. D.: New England J. Med., 205, 536, 1931. (8.) Brown, C. F. G.: Med. Clin. North America, 14, 1243, 1931. (9.) Castellani, A., and Chalmers, A. J.: Manual of Tropical Medicine, Ed. 3, London, Baillière, 1919. (10.) Chinn, B. D.: Food Research, 1, 513, 1936. (11.) Cohen, J.: Arch. Surg., 24, 171, 1932. (12.) Cooley, T. B.: J. Am. Med. Assn., 50, 607, 1908. (13.) Crabtree, J. A., and Litterer, W.: Am. J. Pub. Health, 24, 1116, 1934. (14.) Dixon, C. F., and Deuterman, J. L.: J. Am. Med. Assn., 108, 181, 1937. (15.) Dock, W.: Ibid., 83, 31, 1924. (16.) Dolman, C. E.: J. Infect. Dis., 55, 172, 1934. (17.) Epstein, J. W., and Grossman, A. B.: Am. J. Dis. Child., 46, 132, 1933. (18.) Foreign Letters: (a) J. Am. Med. Assn., 107, 1731, 1936; (b) Ibid., p. 803. (19.) Fraenkel, quoted by Vaughan, W. T., Beck, R., and Shelton, T. S.: Arch. Int. Med., 47, 155, 1931. (20.) Freeman, L.: Ann. Surg., 64, 195, 1916. (21.) Graves, W. R., Dulaney, A. D., and Michelson, I. D.: J. Am. Med. Assn., 92, 1923, 1929. (22.) Henthorne, J. C., Thompson, L., and Beaver, D. C.: J. Bact., 31, 255, 1936. (23.) Hermitte, L. C. D.: Trans. Roy. Soc. Trop. Med. and Hyg., 26, 189, 1932. (24.) Herrick, W. W.: (a) Oxford Med., 5, (Pt. 1) 71, 1936. New York, Oxford University Press; (b) Bull. New York Acad. Med., 7, 487, 1931; (c) J. Am. Med. Assn., 70, 227, 1918. (25.) Holman, W. L.: AM. J. MED. SCI., 189, 436, 1935. (26.) Jordan, E. O., and Burrows, W.: Am. J. Hyg., 20, 604, 1931. (27.) Jordan, E. O., Dack, G. M., and Woolpert, O.: J. Prev. Med., 5, 353, 1931. (28.) Jordan, E. O., and Hall, J. R.: Ibid., p. 357. (29.) Keeney, M. J.: California and West. Med., 33, 502, 1930. (30.) Kline, B. S., and Maschke, A. S.: J. Am. Med. Assn., 98, 528, 1932. (31.) Lanon, W. W., Am. J. Ophth., 18, 950, 1935. (32.) Leading-

ham, R. S.: *Med. J. and Rec.*, 131, 5, 1930. (33.) Lemann, I. I., and Teasley, H. E.: *New Orleans Med. and Surg. J.*, 83, 448, 1931. (34.) Lemierre, A.: *Lancet*, 1, 701, 1936. (35.) Lilley, A. B., and Bearup, A. J.: *Med. J. Australia*, 1, 362, 1928. (36.) Lovett, B. R.: *J. Am. Med. Assn.*, 83, 1498, 1924. (37.) McBurney, R.: *Ibid.*, 100, 1999, 1933. (38.) McLean, S., and Caffey, J.: *Am. J. Dis. Child.*, 42, 1053, 1931. (39.) Mackeen, R. A. H.: *Canad. Med. Assn. J.*, 24, 424, 1931. (40.) Master, A. M.: *J. Am. Med. Assn.*, 96, 164, 1931. (41.) Meyer, M. F., and Roeling, J. C.: *Arch. Ophth.*, 13, 445, 1935. (42.) Riven, S. S., and Applebaum, A. A.: *Ann. Int. Med.*, 4, 1387, 1931. (43.) Salomon, H.: *Klin. Wehnschr.*, 39, 1045, 1902. (44.) Shaughnessy, H. J., and Grubb, T. C.: *J. Infect. Dis.*, 58, 318, 1936. (45.) Shearer, H. A.: *Arch. Ophth.*, 13, 447, 1935. (46.) Shrewsbury, J. F. D.: *Brit. Med. J.*, 1, 280, 1934. (47.) Soifer, J. D.: *Am. J. Obst. and Gynec.*, 16, 889, 1928. (48.) Stewart-Wallace, A. M.: *Brit. Med. J.*, 1, 931, 1936. (49.) Tanner, F. E., and Ramsey, R. J.: *AM. J. MED. SCI.*, 184, 80, 1932. (50.) Thompson, L., and Beaver, D. C.: *Med. Clin. North America*, 15, 1611, 1932. (51.) Vaughan, W. T., Beck, R., and Shelton, T. S.: *Arch. Int. Med.*, 47, 155, 1931.

PEDIATRICS

UNDER THE CHARGE OF
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BIRTH TRAUMA WITH SPECIAL REFERENCE TO INTRA-CRANIAL HEMORRHAGE.

THE injuries that are incurred by the child at birth are not limited to the head nor to the intracranial contents although the latter comprise a very large group. According to Holland⁷ a complete list of the injuries that are seen would include every tissue and organ of the body. However, intracranial injuries are the commonest type of injury and present the most important problems as regards etiology, prevention, diagnosis and treatment. Damage to other than intracranial structures may be enumerated as follows: 1, skin and subcutaneous tissues anywhere but chiefly in the scalp; 2, muscles—most often the sterno-cleido-mastoid; 3, fractures of the bones in the skull, clavicle, humerus and femur in the order of their frequency; 4, separation of epiphyses; 5, rupture of or hemorrhage into abdominal viscera such as the liver or the suprarenal; 6, damage to thoracic viscera which is rare; 7, peripheral nerve injury such as the facial nerve or the brachial plexus; 8, direct injury to or hemorrhage of the eye; 9, injuries to the spinal cord or to the vertebral column. Damage to the spinal cord is a commoner cause of fetal and neonatal death than is generally supposed. It may occur during the forcible extraction of the aftercoming head or large shoulders in head presentations. The statistical figures of this lesion are inaccurate because even where autopsy has been made examination of the cord is neglected.

Intracranial injuries present the most frequent form of birth trauma. In addition, they give rise to the most serious and to the most dangerous symptoms. They result either with normal or with excessive pressure on the head. Normal pressure leaves no observable effect on the head except perhaps a moderate amount of moulding. Excessive pressure may result in excessive change in the shape of the head, overstretching and tearing of the dura mater septa and rupture of certain vessels, or there may be a rise in intracranial pressure sufficient to obstruct the

venous sinuses and cerebral veins and produce cerebral congestion and edema. Adair,¹ in a series of 961 autopsies on new-born infants, found that the largest single cause of death was trauma at birth, and this comprised 31.2% of the cases. Grulee⁵ pointed out that, in examining statistics concerning the new-born, it is extremely difficult to find any which will bear the light of criticism. For the most part this is due to the fact that the figures are based upon the causes of still-births and neonatal deaths. Yet there are many cases of intracranial trauma that do not die. Statistical records of these are rare and often unreliable. While we have some knowledge of the frequency of intracranial hemorrhage as a cause of death, little information is available as regards the actual frequency of occurrence of this complication. Therefore, reports of large groups of deliveries with accurate clinical, laboratory and pathologic records are extremely valuable. The report of Tyson and Crawford¹⁵ may be considered as such. They studied the records of the deliveries at the Philadelphia Lying-in Hospital from October 1, 1927, to December 1, 1929. During this time there were 2256 deliveries. Of this group 78 babies were still-born, a percentage of 3.46. The living births were 2178 with 81 deaths or a mortality rate of 3.71%. Of the 78 still-born infants autopsy was secured on 53, with permission to open the head in 31. In this group there were 11 cases of intracranial hemorrhage or an incidence of 35.4%. Of the 81 deaths occurring after delivery 66 came to autopsy with examination of the brain in 56. Intracranial hemorrhage was found in 18 (32.1%). After careful study of all cases, 16 additional babies were diagnosed as cases of intracranial hemorrhage. These were discharged as cured or greatly improved by treatment. In the total group of 2256 deliveries there were 45 definite cases of intracranial hemorrhage or an incidence of 1.9%. These figures do not include mild cases that were symptomless or had mild symptoms that escaped notice so that the actual incidence of this complication may be somewhat higher.

While many cases are the result of active causative factors which are usually recognizable, some are encountered without any demonstrable cause and are probably due to certain predisposing factors, one or more of which are often present. Bland² pointed out a number of these predisposing influences. The parity of the mother is a very definite factor, as the accident is much more frequent in the first delivery than in subsequent labors. It is said that this is especially true with the birth of male infants, but why this frequency exists is not known. Intracranial damage is prone to occur in prolonged and difficult labor, as is met in contracted pelvis with delivery occurring either spontaneously or otherwise. Judicious instrumental delivery may be less likely to be followed by intracranial damage than unwisely governed spontaneous labor. There is a marked increase of predisposition in technically difficult and imprudent forceps delivery. In complicated breech delivery, especially in cases associated with hasty, unskilled extraction of the after-coming head, damage is likely to occur. This method of delivery is held accountable for a large number of cases of brain injury. The occurrence of intracranial trauma is far more frequent in premature and immature infants. There are several causes for this. One cause is the fragility of the blood-vessels in these children. Another is in complete anatomical development of the strengthening fibers of the tentorium. Immaturity and prematurity are among the chief predis-

posing factors. Difficult delivery of the aftercoming head following version is another frequent obstetrical cause of intracranial injury. The indiscriminate use and excessive dosage of pituitrin to stimulate uterine contractions in the second stage of labor often causes damage to the brain or its membranes. Biochemical changes in the blood and constitutional diseases such as syphilis are often included as predisposing factors, but some observers do not agree on this point although it may be reasonable to assume that a hemorrhagic tendency bordering on the pathologic may be a predisposing factor in some cases.

The most frequent result of intracranial trauma is hemorrhage. The location of this varies. According to Litchfield and Givan¹⁰ supratentorial hemorrhage is the most frequent. This may be over the vertex or under the hemispheres. Subtentorial hemorrhages are next in order of frequency followed by intraventricular hemorrhage, hemorrhage into the brain substance and hemorrhage into the spinal canal. A very lucid presentation of the lesions produced by and mechanism of intracranial injury was given by Holland (*loc. cit.*). He stated that overstretching and tearing of the dural septa followed alterations in the tension of the septa accompanying alterations in the shape of the head. Because of the nature of the attachment of the septa to the cranial bones this is inevitable, and the fact can be demonstrated on a fetal head by reflecting the scalp and removing sufficient of one parietal bone to allow the cerebral hemisphere to be removed and the septa to be viewed from that side. On compressing the head in the suboccipitobregmatic diameter, the head becomes shortened anteroposteriorly by forward displacement of the occipital bone and heightened vertically by bending and elevation of the vault. If at the same time the septa are observed, it will be seen that the middle two-thirds of the falx cerebri and the tentorium will become stretched and tense. In addition, the septa move as a whole as will be appreciated by watching the anterior point of junction between the falx and the tentorium, which is the site of entrance of the vein of Galen into the straight sinus. This becomes displaced upwards and forwards, the latter movement being the much more pronounced. If the pressure is increased by stronger compression, the tentorium tears near its free border just below its junction with the falx. The bending of the bones and the excursion of the vault is resisted by the septa and when the septa tear, a restraining influence is removed. The septa exert a protective influence during labor against excessive alteration in the shape of the head. Reasonable moulding of the head is beneficial, but undue distortion may jeopardize life of the fetus by producing intracranial disturbances, the most important of which is hemorrhage from the overstretching and rupture of certain vessels. The view that the septa are designed to take stress is emphasized by the fact they contain strengthening bands and fibers arranged along the lines where stress is most likely to occur. These bands are developed in order to withstand the effects of excessive stress during labor. There are an anteroposterior and a vertical system. The latter consists of two opposing sets of convergent fibers which meet in their points of convergence. From above downwards fibers converge from the middle two-thirds of the falx, and from below upward fibers from the tentorium converge. They meet in a strong band which has been called the anterior vertical band of the tentorium. This band is subjected to stress in almost every labor, and is the usual site of tentorial tears. This theory

of cranial stress is supported by the tears of the tentorium and falx as found in dead fetuses. Tentorial tears are nearly always situated in what has been described as the area of greatest stress, just below the junction with the falx anteriorly and implicating the anterior vertical band. Tears of the falx cerebri are found relatively infrequently and they usually occupy the middle two-thirds and are elliptical with the long axis lying in the line of greatest stress. The tears may affect one or both sides of the tentorium and may be complete or incomplete. The latter involve only the superficial layers. Complete tears usually involve the free border of the tentorium but sometimes there is a perforation. Tears of the dural septa may bleed very little or not at all and are not always fatal injuries of themselves. They indicate excessive intracranial stress and the mortal lesion may be the accompanying intracranial effects such as cerebral hemorrhage and the asphyxial effects of intracranial pressure.

From the etiologic standpoint there are two varieties of intracranial hemorrhage, traumatic and asphyxial. Gross hemorrhage is probably always traumatic. It occupies the subdural space and is nearly always associated with tears of the dural septa. Asphyxial venous engorgement is a most important contributory factor in traumatic hemorrhage, for engorged veins rupture more easily and bleed more freely. Clear postmortem evidence of fetal asphyxia is usually found in cases of gross hemorrhage. A clear differentiation between traumatic and asphyxial bleedings is not always possible, and they often occur together. Engorgement of the cerebral veins may be part of a general asphyxia, or may be a local condition due to obstruction of the cerebral veins from cerebral compression or traumatic cerebral asphyxia. When large vessels have ruptured it is possible to trace definitely the source of the hemorrhage. Large veins commonly found ruptured are the vein of Galen and the cerebral veins entering the superior longitudinal sinus. Sometimes the venous sinuses themselves are ruptured, the most common one being the straight sinus and more rarely the superior longitudinal and lateral sinuses. The site as well as the size of a hemorrhage is of importance as regards the effect produced. Large hemorrhages kill by compression of the cerebrum with damage to the respiratory centers. Hemorrhage in the posterior fossa or infratentorial hemorrhage is more damaging than elsewhere in the subdural space. In studying the brain itself there are found petechial hemorrhages and small areas of necrosis in a very high proportion of newborn children. The hemorrhages are definitely related to the distribution of the tributaries of the vein of Galen, the vena terminalis, vena lateralis ventriculi and vena chlorioides. Necrotic areas appear as opaque yellowish spots, often in confluent groups, in the central white matter and basal ganglia around the third and lateral ventricles. Microscopic or macroscopic hemorrhages can be found in 95% of infants during the first weeks of life.

Prolonged cranial compression may obstruct the venous sinuses and cerebral veins and produce asphyxia of the brain and medulla. The lesions found at autopsy are intense congestion and edema of the brain and meninges. This still further increases the intracranial pressure. This condition is sometimes classed under the heading of intracranial lesions without hemorrhage but perhaps a better term would be traumatic cerebral asphyxia. The effect of asphyxia on the respiratory

center would be to stimulate it, and the fetus would make intrauterine respiratory efforts. This is evidenced in some cases at autopsy by the finding of amniotic fluid in the trachea or bronchi. The alteration in the intrathoracic pressure as the result of the inspiratory efforts would lead to venous engorgement of the whole venous system or a generalized asphyxia. While such an asphyxia would not necessarily be fatal, if it were prolonged it would lead to increasing paralysis of the respiratory center causing the center to fail to respond to stimuli after delivery.

Although the bones of the cranium are freely movable and although this allows for considerable overlapping or moulding, injury of certain of these bones occur. Hemsath⁶ reported 32 cases of separation of the posterior intraoccipital synchondrosis. He called attention to the fragility of the base of the skull even in the full-term fetus. The synchondrosis between the squamous and lateral portions of the occipital bone, because of its weakness and its close proximity to the medulla oblongata, makes the base of the skull susceptible to grave trauma during delivery. This injury consists of a separation, which may be called an osteodiasis since it is not really a fracture. Hemsath found 32 cases in 166 consecutive autopsies in still-born and neonatal deaths. Osteodiasis was found in 48% of the autopsies on patients delivered by version with breech extraction; in 33% each of forceps deliveries and of primary breech extractions, and in 2.3% of spontaneous deliveries.

The early symptoms of intracranial hemorrhage in the new-born do not present a definite fixed picture. The symptoms vary according to the location, type and extent of the hemorrhage. As regards the extent of the hemorrhage, this varies from very extensive loss of blood to very small bleeding and there are undoubtedly many hemorrhages of such mild type that they are not recognized. Moore¹² gave as the most common early symptom signs of cortical irritability, such as crying, and heightened irritability of the motor centers such as twitching of the muscles, spasticity and convulsions. In some cases of ventricular or subtentorial hemorrhage the infant may be very quiet or even comatose, but usually even in these cases there are some early signs of cortical irritability. These will always tend to dominate the picture, even if the cortex itself is not directly affected by the hemorrhage but where edema or pressure of a hematoma from beneath is producing the irritation. The symptoms vary from mere increase in spasticity of the extremities with occasional twitchings of the muscles to generalized convulsions. Perfectly normal babies may present the former picture at times so that these symptoms alone are not diagnostic. In the average hemispheric case there is twitching or convulsive movement of the lower extremities either unilateral or bilateral. In cases where the hemorrhage is infratentorial the cranial nerves may be involved first with convulsive movements of the facial muscles or of the eye muscles. In cases where the hemorrhage is extensive so that the intracranial pressure is raised markedly there may be a series of general convulsions. These begin with clonic convulsions of the extremities, strabismus, nystagmus, opisthotonos, respiratory disturbance, and loss of consciousness. In some of the ventricular hemorrhages the infant may have tonic convulsions similar to those seen in tetanus. Another important symptom of intracranial hemorrhage is refusal to nurse. This is probably due to a disturbance of the normal nursing reflex, which in the normal infant

is brought out by putting the nipple against the lips. This sometimes occurs also in premature or immature babies so that it cannot be considered as pathognomic although it is always highly suggestive. Disturbance of respiration is a very frequent symptom. This may take the form of very slow breathing or a very rapid breathing or an irregular breathing. Slow breathing is a sign of subtentorial or intraventricular hemorrhage which causes direct irritation or paralysis of the medullary centers. Cyanosis is another frequent symptom. It may be an accompaniment of the respiratory embarrassment due to the direct effect of the hemorrhage or to the cessation of breathing due to a convulsion. In some cases atelectasis is associated with the cerebral injury as a result of the shallow breathing. Signs of increased intracranial pressure such as bulging of the fontanelle and increased pressure of the spinal fluid are often encountered. Minute hemorrhages or subtentorial hemorrhages do not cause bulging of the fontanelle. The increased spinal pressure can be shown only by spinal puncture. Bloody spinal fluid is an absolute diagnostic point provided it can be certain that the blood is not the result of puncture of a vessel in making the tap. The presence of degenerated red blood cells, cellular debris and hematin pigment suggest blood from intracranial hemorrhage while normal appearing cells suggest blood resulting from the spinal puncture. Paralysis is a late sign of intracranial hemorrhage except in the most severe cases. In these cases it is often a terminal symptom. Ocular changes occur but their demonstration is difficult. These consist of mild edematous blurring of the upper and lower margins during the first few days of life with later an edematous blurring of the entire surface of the nerve head and all of its margins. Change in the coagulation time of the blood is another symptom of intracranial hemorrhage. A prolonged coagulation time is a direct indication for the injection of whole blood.

Shannon¹⁴ recognized the confusion frequency of cerebral complications in the new-born with indefinite recognition of the underlying conditions, but with most of the burden placed upon obstetrical error. He called attention to the frequent existence of disturbances which are often responsible for the symptoms of intracranial involvement or may be present together with an actual cerebral trauma.

Other conditions besides trauma give rise to a clinical picture that closely resembles that of birth injury. In fact some of these may be coexistent with the picture of cranial injury. Shannon stated that a constitutional syndrome exists frequently during the neonatal period. This may be independent of obstetric abnormality and is often responsible for the symptoms of cerebral disturbance. This condition is tetany and it may be only a part of a syndrome consisting also of a tendency to generalized edema and of edema of the brain. It may be that the latter is responsible for many of the symptoms usually attributed to cerebral hemorrhage and other injury of the brain. According to Shannon, tetany results from some interference with the calcium metabolism which results in a low ionic calcium content of the blood and tissues. Such causes are excess of sodium and potassium, calcium starvation, parathyroid deficiency and alkalosis. In addition to the symptoms produced by the lowered calcium concentration of the blood of the infant, it is quite possible that the low blood calcium content may favor loss of coagulability of the blood and predispose more readily

to hemorrhage as well as to edema. The cerebral symptoms of tetany are the most important. They are the signs of cerebral pressure. The pulse may be slow, though the slowness may not be constant. It may be noticeable only when the infant is perfectly quiet, the normal rapidity returning almost immediately when the infant is made to cry or is otherwise disturbed. In the extreme phase this process may progress into the cyanotic attack. The latter may come on either by holding the breath while crying or while the infant is perfectly quiescent. In both cases the heart is slowed almost to a complete cessation of its beat and respiration is suspended for a varying length of time, and the infant is to all appearances dead. When recovery occurs, its onset may be heralded by a deep gasping inspiration following which both respiration and pulse assume their normal characters. In some cases the heart beat may become first more rapid and stronger, followed shortly by the faintest respiratory effort, which together with the cardiac action gradually assumes the normal. Usually the cyanosis, which is most extreme during the attack, entirely disappears in the intervals, though this may not always be true. At times when marked tetany is present, it seems that respiratory irregularity may occur as the result of spasm of the diaphragm, similarly to what is noted in other types of tetany. Typical generalized convulsions may occur. Strabismus, pupillary irregularity and spasmodic downward turning of the eyes may be noted also. In cases showing these symptoms the diagnosis of increased intracranial pressure may be supported by a definitely bulging fontanelle. More often the fontanelle is extremely tense, the sutures being separated and the whole cranium giving the impression of an inflated ball. Improvement of the condition follows administration of calcium, and the condition may clear entirely if it is the result of tetany alone. In those cases with cerebral injury present with the tetany, improvement may be only partial.

The diagnosis of intracranial hemorrhage may not be easy. According to Loeber,¹¹ in order to arrive at a diagnosis of intracranial hemorrhage, account must be taken of the history of the delivery, the signs and symptoms of the new-born suggestive of the condition, the recovery of bloody cerebrospinal fluid after puncture and an improvement or relief of the symptoms following the puncture. It is more likely to be found after prolonged labor, precipitate labor, in large or oversized infants and breech extractions alone or following version. Infants born under these conditions and who show signs after delivery of a difficult or abnormal respiration, or those having asphyxia, and those with tense, bulging fontanelles suggest the diagnosis of intracranial hemorrhage. Other suggestive symptoms are a whining, high pitched cry and refusal to nurse or difficulty in nursing. The heart is usually rapid with strong sounds and a full pulse, but cyanosis may be constant or intermittent. There is no real pathognomonic sign unless it be bloody cerebrospinal fluid. Even this may be misleading unless it is certain that the blood in the fluid is not the result of puncturing a vessel in making the puncture. Levinson⁹ and others recommend spinal puncture for the purpose of establishing the diagnosis, but he also considered it of therapeutic value. Loeber, (*loc. cit.*) recommended the cisterna route as the method of choice in obtaining fluid for diagnosis as well as a therapeutic measure because of the ease of access and because the posture of the baby during the procedure does not tend to exaggerate

the already existing trauma and symptoms. In the prevention of birth injury the responsibility is entirely with the obstetrician at least insofar as avoidance of such procedures as are likely to threaten injury to the child is concerned. From all sources it is evident that attempts to hasten the onset of labor, to shorten the duration of labor and to allay pain are large factors in the resulting ill effects to the baby. Galloway⁴ emphasized that nothing should be done to hasten delivery until the head is visible or on the pelvic floor. The use of solution of posterior pituitary and other preparations to cause more rapid descent of the head is firmly contraindicated. Episiotomy is indicated in order to relieve pressure as the head comes through the narrow vaginal opening, especially in cases where the baby is premature. Premature rupture of the membranes either for the induction of or to hasten labor is contraindicated because of the negative pressure exerted on the presenting parts. Application of forceps is contraindicated as it may still further increase the pressure, but outlet forceps in conjunction with episiotomy usually result in fewer hemorrhages. In the use of forceps it is most necessary to have a set-screw or some means to prevent excessive pressure. In cases where there has been excessive moulding of the head of the infant this moulding should be released slowly. All attempts at resuscitation by violent motions with the baby must be avoided. Too prolonged labor also is dangerous. Cesarean section after a moderate test of labor is fairly safe or early in those cases where it is known that delivery through the usual way will be impossible. According to Galloway, breech delivery and version with breech extraction give higher incidence of birth trauma than any other type of delivery. The fetal mortality is also correspondingly high. There are several pertinent facts relative to breech extraction which demand attention. The unnecessary haste displayed by the average operator is most objectionable, and after this the most undesirable factor is the lack of complete relaxation and dilatation of the soft parts. Breech extraction requires complete dilatation and deep ether anesthesia. Episiotomy is indicated in practically every case. Certain fundamental precautions in addition are necessary. The operator should avoid pressure on the fundus, extreme angulation, excessive suprapubic pressure and dangerous traction. The latter is likely to cause damage to the cord.

In the treatment of intracranial birth injuries Kugelmass⁸ stressed primarily the need for gentle manipulation in the asphyxia of the newborn not only because strenuous methods are productive of bodily trauma but also because they either aggravate an already existing intracranial injury or may produce dural injury especially in the premature infant. In the asphyxiated baby the veins are engorged and as a result are more easily damaged as many babies have a tendency towards bleeding. Mouth-to-mouth insufflation is the method of preference for a number of reasons. The procedure is not forcible, the baby's body is essentially at rest and the presence of from 3 to 4% of carbon dioxide in the operator's breath favors the stimulation of respiratory activity. In addition, the Flagg apparatus for the administration of carbon dioxide-oxygen mixture is recommended together with the employment of the Drinker respirator and in some cases the oxygen tent has proved useful. Atropine and alpha lobelin have been recommended as well as other respiratory and cardiac stimulants. Pressure symptoms resulting from intracranial hemorrhage or the marked cerebral edema

often seen as an attendant phenomenon may be alleviated either through the vascular route or through the cerebrospinal canal. By the vascular route relief of pressure is obtained by the intravenous injection of hypertonic glucose solution. By the spinal method pressure is relieved by spinal, cisternal or ventricular puncture. The natural tendency of newborn infant towards hemorrhage or a definite bleeding should be treated by the injection of whole blood into the gluteal areas. Birth shock should be treated by the application of heat; by the administration of fluid with some nourishment if possible. Kugelmass recommends the administration of a solution combination containing 3% of gelatine, 5% of glucose and 0.5% of sodium chloride by the Breck feeder every hour. After the second day evaporated or condensed milk mixtures should be used if maternal milk is not available. The early and prompt improvement of nutrition is essential. Surgical intervention by trephining has resulted in a high mortality rate.

Riesenfeld¹³ recommended posture as a procedure in controlling the intracranial hemorrhage of the new-born, as well as method for the prevention of the condition. In his service all babies are placed in an almost vertical position with the head slightly extended and maintained in this position by small pillows. This position is maintained for from 8 to 10 days. In cases of cerebral hemorrhage it is continued for a longer period. It is claimed by this author that in the upright position the sagittal venous pressure is materially lessened, a fact which has been shown by animal experimentation.

A proportion of the infants that survive intracranial trauma at birth develop and grow with no apparent evidence of the trouble that they experienced during the early days of life. Others in varying degrees are crippled mentally and physically. Carlson and Klingman³ based their report on studies made on persons injured at birth, who were treated at the Neurological Institute of New York. They found that while the pathologic changes underlying the conditions were inadequately defined, the manifold symptoms indicated widespread lesions scattered through most of the nervous system including the spinal cord. It seemed probable that the sensory area and the motor cortex were involved to a greater extent in the choreoathetotic and spastic patient than is usually supposed. The evident influence of such factors as fear, concentration, attention and soft-consciousness in increasing the abnormal movements or posture of certain children definitely indicated the probability of damage to the higher centers and emphasized the necessity for control of these subjective feelings as necessary to effective training of the muscles. They extended their investigations into the field of conditioned reflexes and especially into that of psychic activity. Their results were encouraging and justified the attempts to train or recondition acceptable patients with spasticity and choreoathetosis. In planning treatment, it is necessary not only to estimate the mental level of the patient, but also to eliminate as far as possible such special disabilities as those of speech, hearing and vision. The majority of disturbances of speech concern expressional speech and are a part of the general motor disability. Disturbance of speech was found so closely linked with the general spastic condition that improvement was not possible often until the patient had learned to control the larger groups of muscles. When this coördination was obtained speech improved not infrequently without special training.

REFERENCES.

- (1.) Adair, F. L., Jr.: *J. Michigan Med. Soc.*, 31, 363, 1932. (2.) Bland, P. B.: *New England J. Med.*, 211, 296, 1934. (3.) Carlson, E. R., and Klingman, W. O.: *Med. Clin. North America*, 19, 807, 1935. (4.) Galloway, C. E.: *J. Am. Med. Assn.*, 106, 505, 1936. (5.) Grulee, C. G.: *Am. J. Dis. Child.*, 52, 648, 1936. (6.) Hem-sath, F. A.: *Am. J. Obstet. and Gynec.*, 27, 194, 1935. (7.) Holland, E.: *Ibid.*, 33, 1, 1937. (8.) Kugelmass, I. N.: *Med. Clin. North America*, 15, 1313, 1932. (9.) Levinson, A.: *J. Am. Med. Assn.*, 104, 2243, 1935. (10.) Litchfield, H. R., and Givan, T. B.: *Arch. Pediat.*, 51, 186, 1934. (11.) Loeber, M.: *New Orleans Med. and Surg. J.*, 83, 536, 1931. (12.) Moore, C.: *Nebraska State Med. J.*, 17, 513, 1932. (13.) Riesenfeld, E. A.: *Arch. Pediat.*, 48, 728, 1931. (14.) Shannon, W. R.: *Am. J. Dis. Child.*, 48, 517, 1934. (15.) Tyson, R. M., and Crawford, W. H.: *Am. J. Obstet. and Gynec.*, 21, 694, 1931.

PHYSIOLOGY

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The Intercellular Substance of the Brain Cortex (Nissl's Cerebral Gray). Its Physiological Significance. A. E. TART (Laboratory of Psychiatry, Philadelphia General Hospital). Fifty years ago the presence of an intercellular substance in the brain cortex was much studied and generally acknowledged. More recently, it has been almost entirely ignored both anatomically and physiologically. Intercellular substance in other tissues has received considerable recent attention. Its presence in the developing embryo has been observed and described. It has been demonstrated by a number of investigators that this substance has a close relationship with vitamin C, as shown in scurvy, a condition in which there is lack of its formation. This lack is clinically evident in the test for capillary resistance. In paresis, the alteration of the intercellular substance of the brain cortex has been identified by means of fresh tissue in the dark field by this author, and by others in fixed and stained material. The characteristic microscopic appearance of the brain cortex in paresis has been described as a disturbance of cell lamination, giving a "wind-blown" effect. The relation of vitamin C to malaria treatment of paresis has been studied particularly by Plaut and von Bülow, who found that there is a primary fall with a later rise above the degree which existed before treatment. They also found that vitamin C is present normally in greater amount in the cortex than elsewhere in the brain. The writer has drawn an analogy between this cerebral gray and the proteins of blood serum, which are also intercellular substance. Microphotographs show their similarity of appearance. The physiologic importance is emphasized. Since it has been demonstrated that there are no lymphatics in the brain, it seems probable that this strongly hydrated, finely particulate material acts both as a distributor of brain tissue fluids and as a necessary protection to the brain cells. Microphotographs illustrate normal cortical intercellular substance; a comparison of the cortex in the newborn and more mature rat; comparison of normal and senile cortex and normal intercellular substance compared with that in paresis.

The Relation of Dietary Protein to the Formation and Storage of Gonadotropic Hormone in the Pituitary Gland of the Rabbit. MAURICE H. FRIEDMAN and GERTRUDE S. FRIEDMAN (Laboratory of Physiology, University of Pennsylvania). The pituitary gland of the estrus rabbit contains enough gonadotropic material to cause ovulation in 10 or more rabbits. Copulation causes a rapid and almost complete discharge of the gonadotropic material so that 24 hours postcoitum the gland contains less than enough material to cause ovulation in one rabbit. For several days following coitus, during the rapid growth of the corpora lutea, the pituitary is apparently unable to store significant amounts of the gonadotropic material. At the 6th day postcoitum, however, there is a sharp rise in the gonadotropic content of the gland, to a level about two-thirds of the estrus level, and by the 10th day the estrus level is again attained. These findings confirm the original work of R. T. Hill, and this curve of restitution of the gonadotropic content after coitus was used to determine the effect of various dietary regimes on the rate of formation and storage of the sex-stimulating hormone of the pituitary. It was found impossible to influence this curve significantly by protein restriction, even though the experimental animals were kept on a protein-free diet for 17 days before and 8 days after coitus—a total of 25 days without dietary protein. Despite this protein deficiency, and in the face of loss of body weight, the experimental animals were able to form and store the gonadotropic principle at a rate similar to that of control animals which were on a 16% protein diet, and which were gaining weight at the rate of 200 grams a week.

The Adrenals of Rats After Thyroidectomy and Gonadectomy, Considered in Relation to Pituitary Histology. ISOLDE T. ZECKWER (Department of Pathology, University of Pennsylvania). It is known that when one adrenal is removed, the other undergoes compensatory hypertrophy only when the pituitary is present. It is reasonable, therefore, to search for a type of cell in the pituitary that is responsible for adrenal growth.

In the present experiments, the marked quantitative and qualitative alterations in cellular make-up of the pituitary consequent upon thyroidectomy and gonadectomy did not prevent the normal compensatory hypertrophy of the second adrenal after the first was removed. "Castration cells" and "thyroidectomy cells" can be excluded as cells controlling adrenal growth, as their numbers bear no relation to adrenal weights. Since acidophils are absent or greatly reduced after thyroidectomy, yet compensatory adrenal hypertrophy occurs, acidophils can be excluded as responsible for adrenal growth. In pituitaries of rats both thyroidectomized and gonadectomized there remain, in addition to the two types of cells reacting to these operations, only non-secretory chromophobes and unaltered basophils. By this process of exclusion the suggestion is made that adrenal growth may depend upon a type of basophil that is different from the cells that react to gonadectomy and thyroidectomy. The hypothesis is proposed that there may be distinct types of anterior pituitary cells which cannot be differentiated from each other under normal conditions, but which can be dissociated when the pituitary is altered by ablation of thyroid and gonads.

The Effect of Choline and Sucrose Feeding Upon Liver Glycogen and Lipids. H. M. VARS, S. GOLDSCHMIDT and I. S. RAVDIN (Harrison Department of Surgical Research, University of Pennsylvania). Best and his coworkers² have presented evidence from which they conclude that choline, naturally occurring in the food, is an important factor in determining the level of liver fat produced by diet. Diets which contained little or no naturally occurring choline resulted in a massive deposition of fat in the liver. Choline chloride fed to such animals led to a decrease in liver fat. No satisfactory explanation of the mechanism of this process has been advanced.

Our findings are in agreement with those of Best *et al.*, that choline chloride added to the dietary of rats, whose livers contained about 40 % of total lipids, resulted in a diminution in the fat content. In addition we have shown that accompanying the fall in liver fat the liver glycogen increased. In an animal on an adequate diet increase in the liver glycogen usually results in a fall in liver lipid. Hence the results may be explained either as due to the action of choline in mobilizing liver fat back to the fat depots or in metabolizing it, as Best has postulated, or that possibly the primary effect of choline is to cause a deposition of liver glycogen with the secondary depletion of liver fat as a consequence. Any explanation of the action of choline must take this latter possibility into consideration.

In agreement with Channon³ and later Best,¹ we have found that on a choline-poor diet, in which alcohol-extracted casein is the source of protein, fat is deposited in large amounts in the liver only when the protein calories are below 10 % of the total calories of the diet.

A choline-free diet, in the form of sucrose as the sole source of food to the rat, has given divergent results in our hands. In the larger number of animals the liver fat has decreased and liver glycogen increased. A smaller group conform to the published findings of Best, the liver fat increased, and we have found also a concurrent increase in the liver glycogen. This latter finding is an exception to the rule of the reciprocal relationship between liver fat and glycogen.

Preliminary Report Concerning a Ballistocardiograph. An Analysis of the Record Obtained Under Various Physiologic and a Few Clinical Conditions. ISAAC STARR, A. W. RAWSON and H. A. SCHROEDER (Departments of Research Therapeutics, Pharmacology, and the Johnson Foundation, University of Pennsylvania). The study of the motion imparted to the suspended body by the recoil from cardiac action and the impact from the expelled blood dates from Yandell Henderson's experiments in 1904. Since then Heald and Tucker (1922), Angenheister and Laue (1928), and Abramson (1933) have published records. These records show chiefly the normal form of the curve obtained, the effect of respiration, and of exercise. Our results are similar. The few clinical records published by Abramson are uninforming.

Our instrument consists of a light wooden bed rigidly braced with iron. This is suspended by wires from the ceiling and braced from the lateral wall to limit motion to the longitudinal direction. This bed is held, a little off its low point, by means of a strong steel cantilever spring. A lever, mirror, and optical system magnify the spring's motion about 1000 times at the recording camera. The curve obtained is not

dependent on the spring's period which is more rapid than any of the physiologic waves recorded.

To secure a ballistocardiogram the subject lies on the bed with his feet pressed firmly against a foot plate. Steel weights are added to make the total weight on the bed 200 pounds.

The normal record consists of a brief movement headward (pre-ejection phase) followed by a sharp movement feetward (recoil from ejection), a sharp movement headward (impact from blood striking the arches, head, etc.) and a final movement feetward (impact of blood striking lower portions of body, the wave having previously reached the upper parts). A small wave occurs constantly in diastole, probably due to the motion of the blood filling the heart.

Study of the records of 140 normal subjects at rest and more than 2 hours after a meal shows the following: The average total amplitude per square meter body surface of males is constant from 20 to 45 years of age and then steadily declines in the later decades of life. In women, this function is almost as great as in men at ages between 15 and 25, but it then declines, leveling out after the 25-35 decade to rejoin the declining men's curve at about 55 years.

If one uses the average wave amplitude, per square meter body surface, times mean blood pressure, or this amplitude times blood pressure times pulse rate, the age and sex differences mentioned above still hold. It seems obvious that the normal standards will not be a simple linear relationship.

The ballistocardiogram of cases of heart disease may differ from the normal by diminished amplitude, by abnormal form, or by both.

The auricular wave in cases of block can be clearly seen. The arrhythmias are easily recognized.

Several intraventricular conduction defects have been shown by notching of waves or by doubling of peaks. The one case of acute cardiac infarction examined showed a most abnormal record suggesting ventricular asynchronism.

The records of many cases of hypertension, without known cardiac weakness, have shown an abnormally low amplitude. This has also been found in the one case of neurocirculatory asthenia studied.

Abnormalities have been encountered which have no counterpart in the electrocardiogram or in any other method of cardiac examination.

Microscopic Observations on Extraendothelial Cells of Blood Capillaries. E. R. CLARK and ELEANOR LINTON CLARK (Laboratory of Anatomy, University of Pennsylvania). The development and behavior of extraendothelial or adventitial cells on small blood-vessels have been studied by prolonged microscopic observation of living vessels as seen in transparent chambers installed in the rabbit's ear, with the following results:

Adventitial cells form from fibroblasts or fibroblast-like cells which, in their migration, come in contact with and flatten out on the outside of the capillary wall. This process occurs chiefly during active new formation of blood capillaries—many capillaries receiving adventitial cells even before circulation through them has been established.

At first, they are sparsely and somewhat irregularly distributed on capillaries, have their long axis parallel with the capillary, and manifest slight powers of amoeboid movement, which gradually subsides.

The further development of these outside cells depends upon the fate of the capillary, which may continue as a capillary, become part of an artery or vein, or retrogress. If it remains a capillary, the number of adventitial cells usually remains unchanged, although there may be an occasional increase in number by mitotic division. If it becomes part of an arteriole the number of cells increases rapidly—in part, at least, if not exclusively—by mitotic division of cells already present, until, by the end of not more than 6 days, there may be a continuous layer of outside cells; meanwhile the axis of the cell changes from longitudinal to transverse. If it becomes part of a venule, the number of cells increases somewhat, and the axes of a majority of the cells remain longitudinal. Around larger venules there may be a development of a capsule-like network from surrounding connective tissue. If a capillary retrogresses the adventitial cell is left behind in the tissue as an apparently inert, small cell, whose fate has not been followed.

If an artery diminishes in size, reduction in the number of outside cells occurs.

The adventitial cells on capillaries and small venules have shown no evidence of contractility. On arteries and arterioles, definite contractility develops in the transverse cells which have become smooth muscle cells, providing a vasomotor nerve has reached them. Such contractility may be manifested in arterioles which are 9 days old, as described in a previous article.

It is suggested that the term "Rouget" cell be given up, and, in its stead, the name "adventitial" cell be substituted—a return to the term "cellules adventicées" employed by Rouget.

REFERENCES.

- (1.) Best, C. H., and Channon, H. J.: *Biochem. J.*, 29, 2651, 1935. (2.) Best, C. H., and Huntsman, M. E.: *J. Physiol.*, 83, 255, 1935. (3.) Channon, J. H., and Wilkinson, H.: *Biochem. J.*, 29, 350, 1935.

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THE
AMERICAN JOURNAL
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AUGUST, 1937

ORIGINAL ARTICLES.

THE EFFECTS OF PROTAMINE INSULIN AND RELATED COM-
POUNDS IN NORMAL AND DEPANCREATIZED DOGS.*

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SINCE the introduction of protamine insulin by Hagedorn, Jensen, Krarup and Wodstrup,² there have been many clinical confirmations of the findings of these authors. The observations to be presented here illustrate some of the characteristics of the action of protamine insulin, zinc insulin and protamine zinc insulin which are revealed by their use in normal and depancreatized dogs.

Methods. The protamine insulin used in the experiments to be described was very kindly supplied by the Connaught Laboratories of this University through the courtesy of Drs. D. A. Scott and A. M. Fisher. The protamine used was prepared from the testes of a species of Pacific salmon—"Onchorhynchus tshawytscha." The insulin was made up in a concentration of 40 units per cc. to which the protamine was added in the proportion of 0.8 mg. per 100 units of insulin. The amounts of zinc which were added to the insulin and to the protamine insulin will be described later.

Blood-sugar estimations were made upon venous blood by a modification of the Shaffer-Hartmann method. Sugar values were determined upon urine samples by diluting 1 cc. urine 200 times and making estimations upon 5 cc. aliquots by the modified Shaffer-Hartmann method.

Female dogs were depancreatized for use in these experiments by means of a one-stage operation under ether anesthesia. No experiment was carried out on these animals until at least 2 weeks after pancreatectomy. During

* A preliminary report of these results was presented by one of us (R. B. K.) at the Annual Meeting of the Society for Clinical Investigation, May, 1936, and published in the Journal of the Society (J. Clin. Invest., 15, 450, 1936).

the period of experiment, the animals were fed a constant daily diet consisting of the following foods and divided into 2 or 3 feedings as indicated in the text; 400 gm. beef muscle (all visible fat removed), 200 gm. beef pancreas, 50 gm. cane sugar, 25 cc. tomato juice, 2 cc. cod-liver oil. To this diet in the later experiments 5 gm. of powdered yeast (Mead Johnson) were added.

Protamine Insulin in Normal Dogs. The effect of protamine insulin in various doses upon the fasting blood sugar of normal dogs illustrates very well the prolonged action of this compound. Experiments were carried out upon the same normal dog at intervals of not less than 5 days. During the time between experiments the animal was fed a diet of dog biscuits and meat scraps. On the day before an experiment, 17 to 18 hours prior to the injection of the insulin on the following morning, the dog was given a meal of lean beef and was then fasted until the end of the experiment. Water was provided *ad libitum*. The insulin was injected subcutaneously at or about 9.00 A.M. and blood sugars were determined at various intervals.

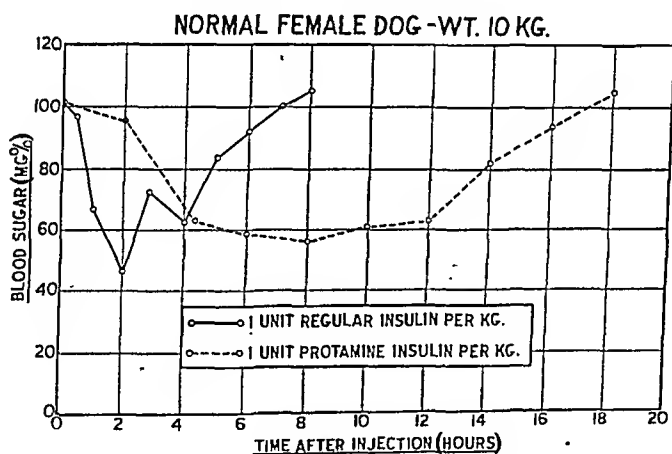


FIGURE 1

The results charted in Figure 1 illustrate the effect upon the blood sugar of a dose of 1 unit per kilogram of body weight of protamine insulin and of a similar dose of regular insulin. The effect of the regular insulin persists for about 6 hours whereas in the case of protamine insulin the blood sugar did not return to normal until 18 hours after injection. The difference in the rate of fall is also to be noted, that following protamine insulin being considerably slower than that produced by regular insulin.

In Figure 2 the results of various doses of protamine insulin upon the blood sugar of a normal fasting dog are shown. There is a marked difference in the amount of protamine and regular insulin which can be tolerated by a normal dog without demonstrating a hypoglycemic

reaction. In these experiments a dose of 2 units of regular insulin per kilogram of body weight produced convulsions whereas 4 units of the protamine preparation per kilogram was the smallest amount required to elicit a hypoglycemic reaction.

When hypoglycemic reactions occur following the administration of protamine insulin they usually appear many hours after the injection. In the experiments, the results of which are depicted in Figure 2, the reaction following the injection of 4 units of protamine insulin per kilogram did not take place until 28 hours after the insulin had been given.

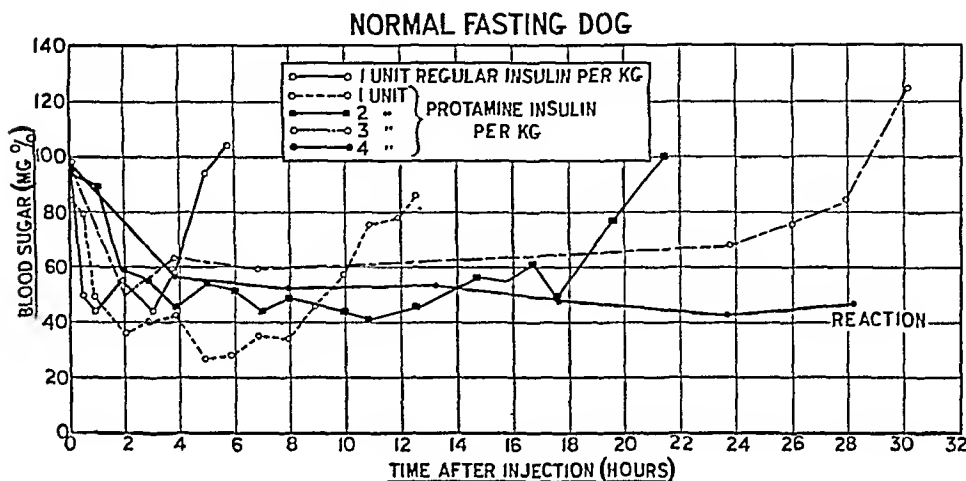


FIGURE 2

Up to a point the effect of increasing the dose of protamine insulin is seen to be that of prolongation of its action rather than a further depression of the blood sugar. It is extremely interesting that the blood sugar can be depressed for such long periods of time without the development of hypoglycemic reactions. In one experiment, it is to be noted that the blood sugar remained at a low level for 27 hours with no more evidence of hypoglycemia than a slight disinclination on the part of the animal to move about actively.

It has been noted in confirmation of the results of the Danish investigators that there is no appreciable difference between the effects of regular and protamine insulin upon the blood sugar when the insulin is administered intravenously.

Protamine Insulin in Depancreatized Dogs. The glycosuria and blood-sugar levels have been observed in depancreatized dogs receiving the two types of insulin.

Studies on Glycosuria in Depancreatized Dogs. Observations on 4 female depancreatized dogs were carried out to determine the extent of the glycosuria when the animals were receiving similar doses of regular or protamine insulin. The diet and amount of insulin were maintained at a constant level. The insulin was

injected subcutaneously daily at 9.00 A.M.; feedings were given at 10.00 A.M. and 4.00 P.M. The urine was collected in 24-hour specimens without catheterization.

Table 1 shows the results obtained from these experiments. The urinary sugar values represent the daily average for 7-day periods. The marked diminution in glycosuria when protamine insulin is being given is obvious.

Acetone appeared in traces in the urine during the period in which regular insulin was administered, but was absent during the period of treatment with protamine insulin.

TABLE 1.—GLYCOSURIA IN DEPANCREATIZED DOGS WITH REGULAR AND PROTAMINE INSULIN (ONE DOSE DAILY).

Dog.	Regular insulin.		Protamine insulin.	
	Dose of insulin (units) 9.00 A.M.).	Sugar excretion (gm.) (daily average 7 days.)	Dose of insulin (units) (9.00 A.M.).	Sugar excretion (gm.) (daily average 7 days).
"M" . . .	17	40.9	17	1.0
"R" . . .	26	13.2	26	1.7
"P" . . .	34	56.1	34	5.6
"B" . . .	30	48.3	30	2.7

Studies on Blood-sugar Levels in Depancreatized Dogs. One of the most dramatic effects of protamine insulin is its ability to maintain a normal level of blood sugar in a depancreatized dog which is receiving only one dose of the preparation daily. This is quite impossible with regular insulin. The use of protamine insulin in this manner was suggested by the findings in normal dogs in which the blood sugar was found to remain at subnormal levels for 24 hours or longer after one injection of protamine insulin.

The results of one experiment are given in Figure 3. In this graph the blood-sugar levels of a depancreatized dog throughout a 24-hour period following one dose of regular insulin and a similar dose of protamine insulin are shown. The insulin was given at 9.00 A.M. followed by feedings at 9.30 or 10.00 A.M. and at 4.00 P.M. The periods depicted, in each case, followed after several days of similar treatment, so they are representative of the condition of an animal which had been stabilized on the particular routine employed.

The high fasting level of the blood sugar with regular insulin is to be noted. There is a rapid fall to a low value and subsequent return to a high level by the end of 24 hours. This demonstrates the rapid onset of action of regular insulin with failure to control the blood sugar for a period longer than 6 to 8 hours even with large doses. With protamine insulin a much more constant level of blood sugar is obtained. A low fasting blood sugar occurs in the morning, to be followed by a slight rise after the morning feeding. The afternoon feeding produces no effect upon the blood sugar and a normal fasting level is obtained on the following morning.

Similar experiments have been performed in which feedings have

been given at approximately the same intervals as adopted by human subjects. There were no essential differences in the results.

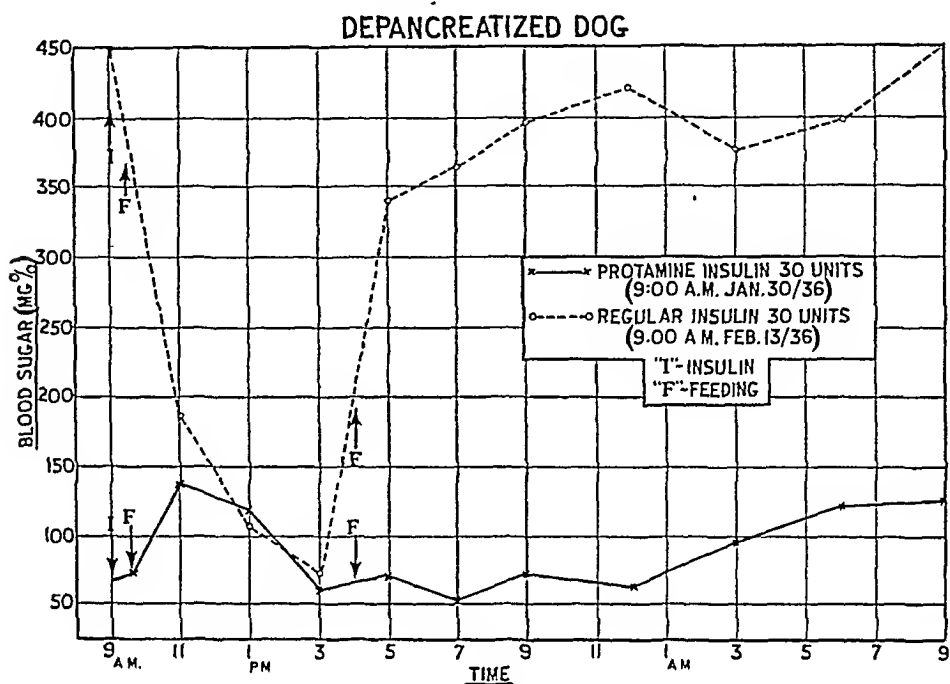


FIGURE 3

Zinc Insulin in Normal and Depancreatized Dogs. Scott and Fisher³ reported that the addition of zinc salts to insulin prolonged the hypoglycemic effect of this hormone in rabbits. Their findings have been confirmed in normal and depancreatized dogs.

The zinc insulin used in these experiments was very kindly supplied by Scott and Fisher. It was prepared by the addition to regular insulin (40 units per cc.) of zinc chloride to make a concentration of 9 mg. zinc metal per 100 units.

Figure 4 represents a comparison of the hypoglycemic effect of regular and zinc insulin in a normal dog. The effect of the regular insulin is complete in 5 hours, while that of the insulin to which the zinc has been added continues for 19 hours. The onset of the depression of the blood sugar in the case of the zinc insulin is very slow compared to that of either regular or protamine insulin.

Figure 5 illustrates the results of experiments designed to compare the action of zinc insulin and regular insulin in a depancreatized dog. The blood sugar during the 24-hour period when one dose of regular insulin is given shows a marked "swinging" character, while that with zinc insulin is more constant. There is considerable rise during the period of feeding, but the blood sugar attains a normal value 24 hours later. The rise during the feedings is probably attributable to the slow onset of action of the zinc insulin.

Relation of Zinc to Protamine Insulin. In collaboration with Scott and Fisher and in extension of their work on rabbits, additional evidence of the importance of zinc in the protamine insulin compound has been secured. Preparations of insulin and protamine,

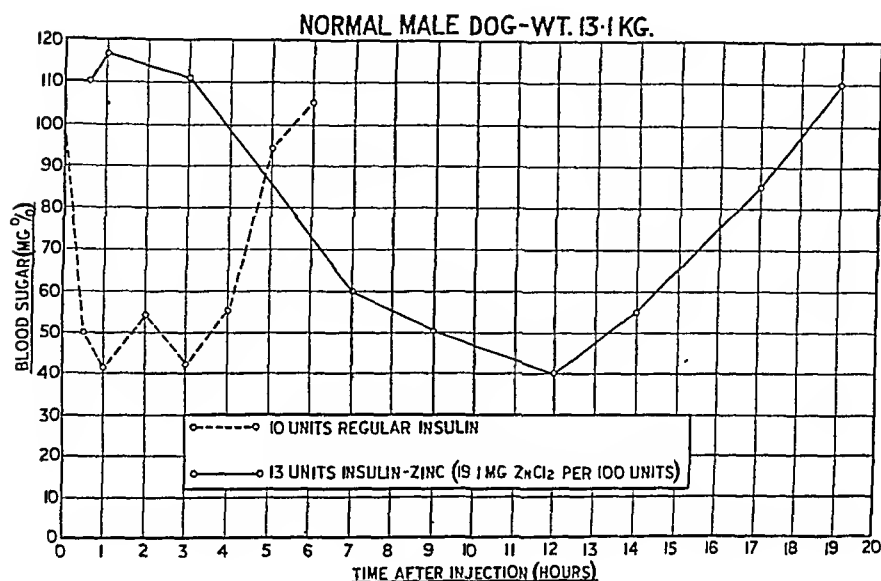


FIGURE 4

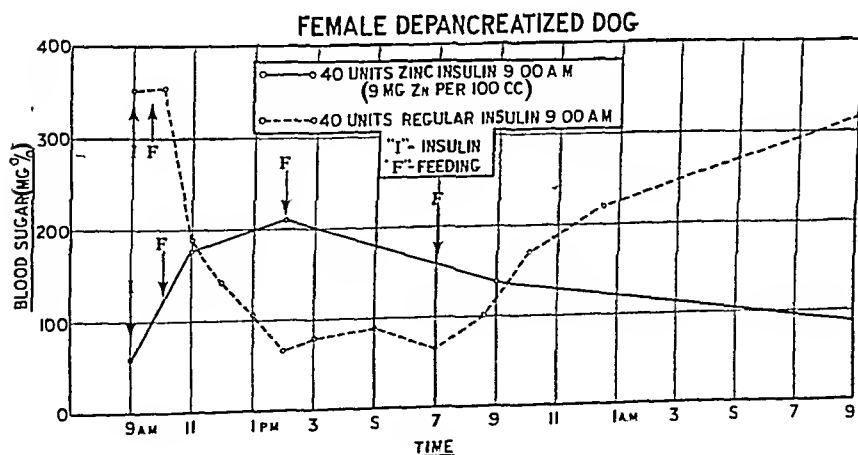


FIGURE 5

made by these investigators by electrodialysis, were very nearly "ash-free." When these substances were combined in a buffered solution a precipitate was formed not unlike that produced upon combination of the cruder materials. However, upon injection into

normal dogs it was found that this "ash-free" compound did not possess the same ability to prolong the hypoglycemic action of insulin as did the cruder substances. The more prolonged effect was restored to the "ash-free" preparations by the addition of a very small amount of zinc chloride, in the proportion of 1 mg. per 500 units of insulin.

Figure 6 illustrates the results of one of these experiments. The first two curves show a comparison between the effects of regular insulin and regular insulin to which the small amount of zinc chloride has been added. The two curves to the right show the prolongation of action produced by the addition of the zinc chloride to the "ash-free" preparations. The mechanism of this action is not as yet clear, but it is probable that zinc or a related metal is responsible in some manner for the moderately stable linkage between insulin and protamine.

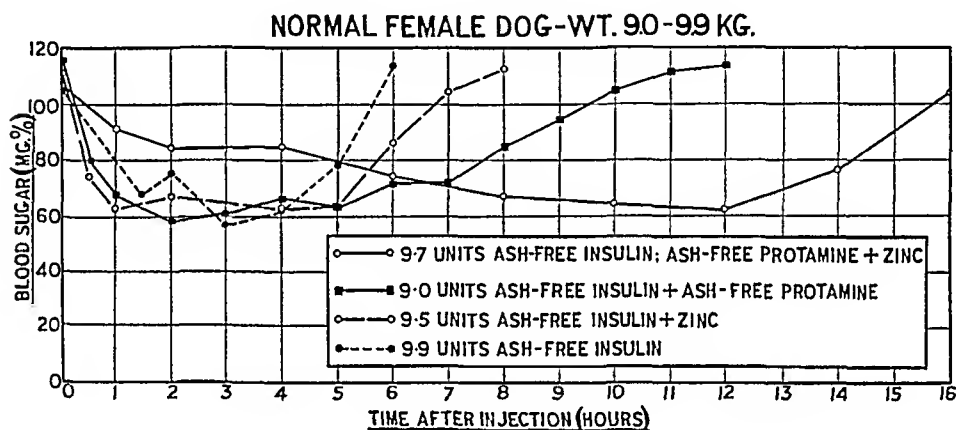


FIGURE 6

Experiments With Protamine Insulin Mixture With 15% "Free Insulin" Present. In a previous experiment it was noted that there was a marked difference in the rate of fall of the blood sugar following the administration of protamine and regular insulin. This no doubt accounts for the postprandial rise of the blood sugar after the morning meal, noted in the case of depancreatized dogs (Fig. 3) and in some clinical cases (Campbell, Fletcher and Kerr¹).

It has been shown that protamine insulin usually contains little or no "free insulin" in the supernatant fluid after separation of the protamine-insulin precipitate. It is probable that the delayed fall of the blood sugar with protamine insulin is due to the slow liberation of insulin from the compound. If, however, some "free insulin" were available the slow onset of the action might be avoided.

Scott and Fisher have found that by reducing the amount of protamine in the mixture some of the insulin remains "free" and can be recovered from the supernatant fluid. Thus by using one-half the amount of protamine, *i. e.*, 0.4 mg. protamine per 100 units, some 15% of the insulin remains uncombined.

In Figure 7 the effect of this mixture upon the blood sugar of a normal dog is compared with that of regular insulin and protamine insulin containing the usual quantity of protamine (0.8 mg. per 100 units). All three preparations contained a small amount of zinc (1 mg. per 500 units). It is seen that the rate of fall of the blood sugar during the first few hours corresponds very closely in the case of regular insulin and the "free insulin" mixture. The onset of action of the protamine zinc insulin is slower than is usually the case. The length

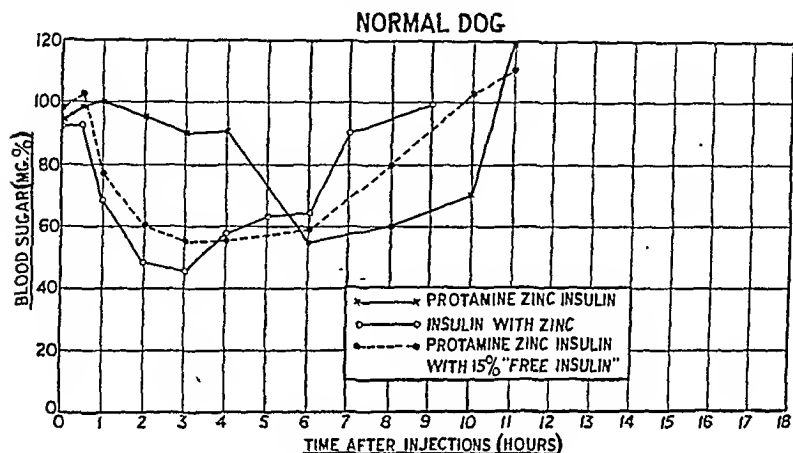


FIGURE 7

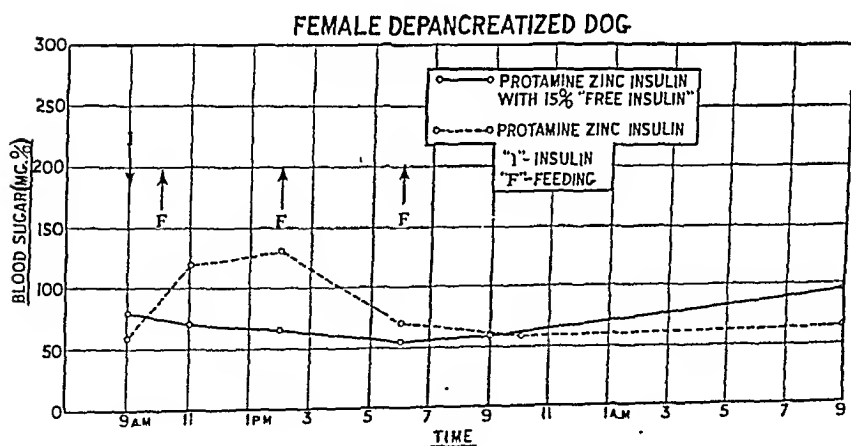


FIGURE 8

of action of the preparation containing the "free insulin" is slightly less than that of the standard protamine zinc insulin. There is considerable individual variation in the response of animals to these preparations.

In Figure 8 the ability of the preparation containing "free insulin" to prevent the postprandial rise of the blood sugar is demonstrated.

The results depicted here show a comparison of the effects of the two preparations of protamine zinc insulin upon the blood sugar of a depancreatized dog to which three feedings of a mixed diet have been given as indicated.

It is not yet possible, however, always to maintain a fixed amount of insulin free in the protamine insulin mixture. Variable results are therefore obtained. Some further work will be required before a preparation providing both free and combined insulin can be recommended for clinical trial. Further results of the use of this preparation in depancreatized dogs will be reported shortly.

Discussion. The response of the normal dog's blood sugar to an injection of protamine insulin reveals many points of interest. The long period of time during which the blood sugar is maintained at a fairly constant low level suggests that some mechanism such as the liberation of glucose by the liver is successfully combating the effect of the slowly released insulin. This effect may be produced by means of the secretion of adrenalin which is known to occur when the blood sugar reaches low levels.

The greater tolerance of the normal dog to protamine insulin than to regular insulin without the occurrence of hypoglycemic reactions is demonstrated in one of the experiments. It has been shown that an animal will remain in an apparently normal condition even though the blood sugar is depressed to levels which are usually regarded as productive of signs of hypoglycemia, such as incoördination, unconsciousness and even convulsions.

If it is postulated (1) that the signs of hypoglycemia are elicited when the sugar content of the fluid bathing cells of the central nervous system has been lowered to a certain level, and (2) that the lowering of blood sugar is due, in part, to utilization of sugar by the tissue cells generally, a rational explanation of the lower level of blood sugar at which the signs of hypoglycemia are observed with protamine as compared to regular insulin may be advanced. The sugar content of the tissue cells (and that of the fluid bathing them) will always be lower than the blood-sugar level. This discrepancy will be greater when sugar is being used rapidly under the influence of insulin which is quickly absorbed (*i. e.*, the blood sugar will be higher when the critical level of sugar in the cells of the central nervous system is reached) than when the tissue cells are stimulated less vigorously by insulin which is absorbed much more slowly. Under these latter conditions, when the concentration of the absorbed insulin in the blood and tissues is presumably lower than when regular insulin is used, the blood sugar will follow more closely the fall in tissue sugar and will, therefore, be lower when the critical level in the central nervous system is reached.

While fewer hypoglycemic reactions are observed in depancreatized dogs treated with protamine insulin than with regular insulin, the reaction produced by the slowly absorbed compound is

much more prolonged and much more difficult to alleviate. In 2 cases we have not been able successfully to combat the effects of hypoglycemia (which developed during the night and was therefore untreated for perhaps 8 to 10 hours) by the intravenous administration of dextrose. While the blood sugar was maintained at a high level by this treatment the animals continued to exhibit signs suggestive of a lesion of the central nervous system. They became progressively weaker and died about 48 hours after the first signs were noticed. While there is no doubt that the hypoglycemic reaction could have been completely alleviated if it had been promptly treated, it would appear that it is much more dangerous to postpone treatment of hypoglycemia resulting from the use of protamine insulin than that produced by regular insulin in comparable doses. When very large doses of regular insulin are used and the hypoglycemia is not treated for from 8 to 10 hours the situation is similar to that observed with protamine insulin.

Very little further comment on the effect of zinc insulin or of protamine zinc insulin in depancreatized dogs is required. It should be noticed that the contrast between the protamine insulin and protamine zinc insulin has been produced by the use of preparations of protamine and insulin in which the ash content has been greatly reduced. While some preparations of protamine insulin may contain such amounts of zinc or related metal that the addition of more metal is without pronounced effect on the duration of the antidiabetic action, this is frequently not the case. Protamine zinc insulin preparations are much more stable than the protamine insulin complex without added zinc (Scott and Fisher³).

The use of protamine insulin in depancreatized dogs has made possible experiments in which there is presumably a fairly regular liberation of insulin throughout the 24 hours. It is possible that further investigations on the action of insulin will be facilitated by the use of this compound.

Summary and Conclusions. The duration of effect of protamine insulin and regular insulin upon the blood sugar of depancreatized dogs has been compared. The rate of fall of the blood sugar with regular insulin is much greater than that with the protamine compound. The duration of the action of protamine insulin is much greater than that of regular insulin. The blood sugar of the normal dog may be maintained at a low level for much longer periods without production of the hypoglycemic reaction than is possible when regular insulin is used.

One dose of protamine insulin daily in depancreatized dogs is sufficient to keep the animal approximately sugar free. When the same amount of regular insulin is used in one dose there is a very heavy glycosuria.

The relatively steady level of blood sugar in depancreatized dogs with one dose of protamine insulin a day is in marked contrast with that observed when one dose of regular insulin is used.

Zinc insulin administered subcutaneously to dogs is apparently not readily absorbed but its action persists for prolonged periods. Additional evidence of the effect of zinc on the combination of protamine and insulin is presented (confirming Scott and Fisher).

The results of preliminary experiments, in which protamine zinc insulin mixtures containing some "free insulin" were used, are described. This preparation exerts a rapid effect which may also be almost as prolonged as that of similar mixtures which contain no "free insulin."

We are indebted to our colleagues, Dr. D. A. Scott and Dr. A. M. Fisher, for their kind coöperation. Some of the more recent experiments have been carried out with the help of Mr. E. A. Dobson.

REFERENCES.

- (1.) Campbell, W. R., Fletcher, A. A., and Kerr, R. B.: *AM. J. MED. SCI.*, 192, 589, 1936. (2.) Hagedorn, H. C., Jensen, B. N., Krarup, N. B., and Wodstrup, I.: *J. Am. Med. Assn.*, 106, 177, 1936. (3.) Scott, D. A., and Fisher, A. M.: *J. Pharm. and Exp. Therap.*, 55, 206, 1935.

INVESTIGATION ON VOLUNTEERS INFECTED WITH THE INFLUENZA VIRUS.

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IN order to determine the rôle played by the influenza virus in the etiology of epidemic influenza it is essential to study the infectivity of this virus for man under experimental conditions. If direct inoculation of the virus into human beings caused a disease which possessed the clinical, immunologic and epidemiologic characteristics of influenza a convincing argument in favor of the virus theory would have been presented.

The first attempts to infect man with the influenza virus were carried out by Andrewes, Smith and Laidlaw.¹ Two hospitalized volunteers were inoculated intranasally with 2 cc. of a filtrate of the respiratory tract washings from infected ferrets. Neither volunteer developed symptoms of influenza. Since blood sera obtained from the 2 patients, even before the attempted infection, contained neutralizing antibodies for the influenza virus, the negative results were regarded by the authors as being due perhaps to the insusceptibility of both volunteers to influenza. Other possi-

bilities considered to explain the failures were that ferret-passage may have attenuated the virus for man or that, as in the case of swine influenza, clinically characteristic human influenza may result only when the virus is accompanied by a second organism.

Experimental. During the period April to October, 1936, we conducted experiments in which human volunteers were inoculated either with the virus isolated during the last outbreak of influenza in Leningrad² or with the WS strain kindly sent to us from London by Andrewes, Laidlaw and Smith.

Materials and Technique of Inoculation. The total number of volunteers inoculated with the virus was 72. We also observed as a control group 12 persons inoculated with lung suspensions of normal mice. Forty-three of the volunteers were hospitalized for 15 to 20 days for clinical and laboratory investigation in the Therapeutic Clinic of the First Leningrad Medical Institute (Director, Prof. M. D. Tushinsky), and 29 in the contagious ward of the Central Military Hospital.

The method of inoculation was by inhalation of atomized suspensions, as in our previous investigation with Pfeiffer's bacillus.³

The material for inoculation in all experiments consisted in a 10% suspension of the lungs of white mice which had been infected intranasally with a lethal dose of the virus adapted to ferrets and mice. Mice furnishing virus were killed 2 days after inoculation. As our investigations have shown, the lungs at this stage are particularly rich in virus, 1 cc. of a 10% suspension containing 10^5 to 10^6 minimal lethal doses for mice. Only those lungs were selected for experimental purposes which on bacteriologic test showed no more than 5 saprophytic microorganisms to 1/20th part of the lung (*i. e.*, 100 bacteria in the entire lung). Some of the lungs (20 to 30%) were bacteriologically sterile. After careful trituration of the selected lungs with 10 volumes of physiologic saline in a mortar with sterile sand, 5 minutes' shaking with beads, and slight centrifuging, a homogeneous suspension was obtained for use in inoculation.

For inoculation by inhalation, the face of the volunteer was covered with a mask of the type used for ether-chloroform anesthesia, through the opening of which was passed the end of the outlet tube of a glass atomizer. In some of the later experiments, inoculation was carried out by means of a gas mask, the crimped tube of which was fastened to a small chamber in which the atomizing was effected. Into the glass atomizer were poured 10 to 15 cc. of the virus suspension. Air from an electric air-pump reduced the suspension into fine droplets which were introduced as a vapor into the mask, from which it was inhaled into the respiratory tracts of the volunteers. Inhalations were carried out for 15 to 60 minutes, during which each volunteer inhaled from 10^5 to 10^6 minimal lethal mouse doses of virus.

Symptoms Developing After Introduction of Influenza Virus Into the Respiratory Tract. Clinically, the most typical signs and symptoms shown by inoculated volunteers were as follows:

Hyperemia of the nasal mucosa and edema of the turbinates, lasting from 4 to 10 days, was observed in 40% of the volunteers. In certain cases this was accompanied by slight cyanosis with dilation of the capillaries. In about 20% of the inoculated persons considerable exudation of mucus from the nose was observed, beginning on the second or third day after inoculation and continuing for 3 to

10 days. At first the exudate was clear; then it gradually thickened, turning into a viscous mucus, but rarely of a purulent appearance. Sometimes symptoms of hyperemia and dryness of the nasal membranes with crusts predominated. Subjectively this was expressed by an increase in the sensation of dryness in the nose and throat and by difficulty of nasal respiration.

Three of the 72 volunteers suffered nosebleed. Hyperemia of the throat was noted in 28% of the cases, accompanied by a swelling of the tonsils, which in 2 cases developed into the signs and symptoms of follicular angina. In the larynx a slight hyperemia of the true vocal cords was occasionally observed, lasting from 1 to 5 days. The supra- and infra-orbital foramina were involved in 21 of the volunteers, as manifested by an irritation of the first and second branches of the trifacial nerve.

General symptoms, in response to inhalation of the virus, were observed in about one-third of the volunteers, while about one-fifth (14 cases) showed a whole series of clinical reactions identical with the most constant symptoms of epidemic influenza. Within 4 to 18 hours after inhalation the temperature rose to 37.5 to 39.0° C., with chills. The temperature reached its highest point within the first few days after inhalation and remained at this level, on the average, for 2 days. There was an acceleration of the pulse parallel to the rise in temperature. The experimental patients complained of headache, localized chiefly in the forehead, of rheumatic pains in the body and pains in the joints, cold in the head, or a congestion of the nose. In a portion of the patients we observed cough, pain upon moving the eyes, sleeplessness, liquid stool, and, in one instance, vomiting.

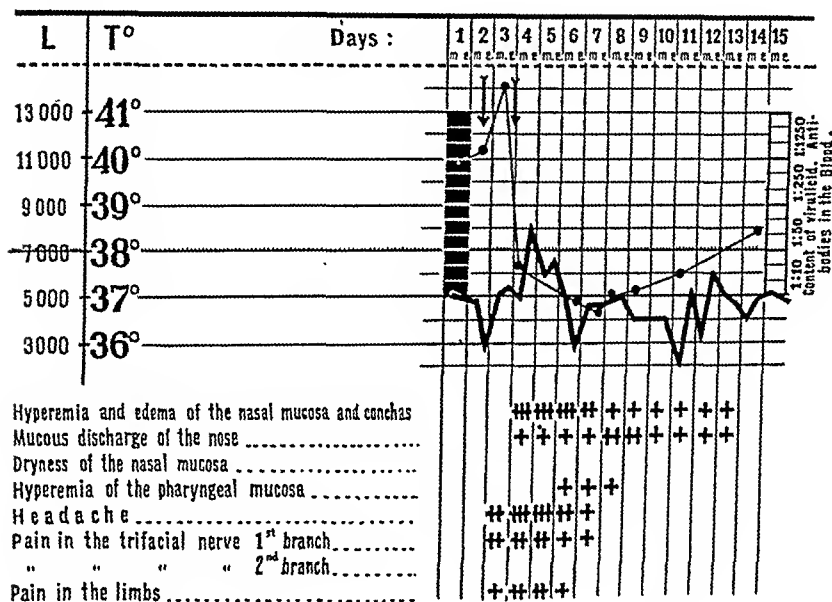
Abstracts of two representative cases follow:

Volunteer P. (Chart I), aged 18, admitted to the Clinic on May 5, 1936, showed no abnormalities in the internal organs or the upper respiratory tract. He was subjected on May 9 and 10 to repeated inhalations of the virus (2 inhalations of 15 minutes each). On May 11, 18 hours after the second inhalation, he had a severe chill. The temperature rose rapidly to 38.3° C. The patient complained of a severe headache in the region of the forehead, pain upon moving the eyes, rheumatic pains in the extremities and joints, cold in the head, and a slight, dry cough. He had a feverish appearance: red, shiny eyes and moist, reddish skin. The nasal mucosa contained a moderate quantity of clear mucus, and the throat showed slight hyperemia. The patient felt pain on pressing in the region of the supra-orbital fossa. Pulse 120. Heart and lungs normal; tongue moist and coated; abdomen soft and without pain. During the night of the 11th the patient was delirious; on the 12th his temperature fell to 37.8° C. There was profuse perspiration. On the third day of illness, a considerable improvement set in. The temperature fell to normal. The headache and cold in the head continued. The nasal mucosa showed pronounced hyperemia but there was no exudation from the nose. Within a few days the headache ceased, and an exudation of thick mucus from the nose developed, which continued during the rest of the patient's stay at the Clinic. The congestion and swelling of the nasal membranes gradually decreased. The hyperemia

of the throat disappeared 4 days after inhalation. A blood examination (Chart I) showed changes typical of epidemic influenza. The volunteer was discharged May 23.

CHART I.

P - va L.



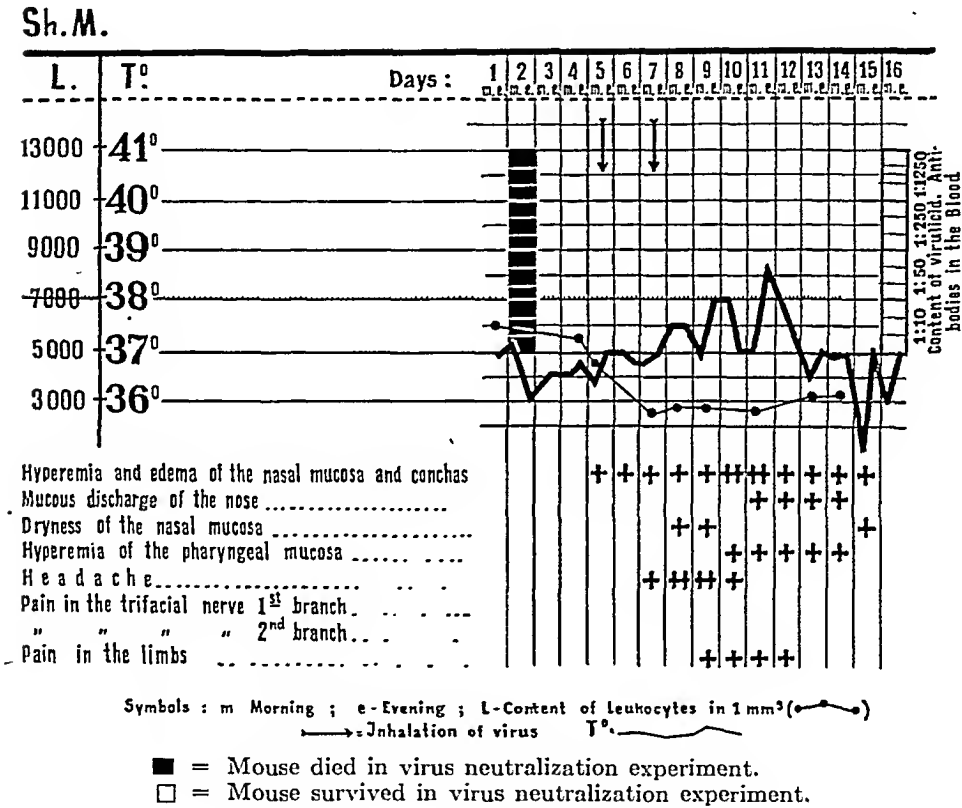
Symbols : m - Morning ; e - Evening ; L - Content of leukocytes in 1mm³ (—●—).
 ——— Inhalation of virus .. T° = ———

■ = Mouse died in virus neutralization experiment.
 □ = Mouse survived in virus neutralization experiment.

The second case presents complications of short duration. *Volunteer Sh. M.* (Chart II), admitted to the Clinic May 25, showed no abnormalities in the internal organs or upper respiratory tract, with the exception of a slight deformation of the nasal septum. The patient was subjected to two 30-minute inhalations of the influenza virus on the 29th and 31st. On June 1, the day after the second inhalation, she complained of a headache in the region of the forehead, congestion of the nose, and a slight, dry cough. Temperature 37.5° C., flushed face, intense hyperemia of the conjunctivae and the nasal membranes, edema of the turbinates, and an accumulation of crusts in the lower nasal passages. Pulse 120, tone of the heart weakened. Respiration was difficult, with dry, whistling râles in the left lung under the angle of the scapula. There was no abdominal pain. On June 2 the patient felt worse. She complained of pronounced weakness and rheumatic pains throughout the body. Temperature increased to 37.6° C. Sputum was expectorated. Symptoms in the upper respiratory tract remained the same. The left lung under the angle of the scapula revealed a small section with moist and dry râles. Stool was retarded. On the 3d, shooting pains under the left scapula and increased coughing were noted. Temperature was 38.6° C. Hyperemia of the nose was more pronounced; edema of the turbinates continued, but with no exudation. In the lungs to the left under the scapula there was a shortening of the percussion tone, with a strengthening of bronchophony. Auscultation revealed moist and crepitant râles at the height of inhalation. On the 4th, general weakness, prostration

and an intensification of the head cold were observed. Temperature was 38.0° C. Hyperemia of the nose and edema of the turbinates were without change, but a small amount of thick mucus appeared. Membranes of the throat showed slight congestion and moistness. During the next few days the temperature fell to normal. The symptoms in the upper respiratory tract and lungs gradually disappeared. When discharged, the patient showed considerable exacerbation of the pain in the joints. Blood examination indicated a distinct leukopenia coupled with a considerable increase in specific virus-neutralizing antibodies.

CHART II.



The 12 persons in the control group, inoculated with suspensions of lungs from normal mice, exhibited no evidence of illness and remained clinically normal throughout the period of observation.

The Blood Picture During Experimental Virus Influenza. White blood cell counts of all volunteers were taken 2 to 3 times before inoculation and 5 to 9 times during the course of the first few days after inhalation.

Of the 72 volunteers, 25 (34%) reacted to inhalation with a decrease in the white cell count to less than 6000 per c.mm. One-third of this group showed leukocytosis for one day, changing during the subsequent days to leukopenia. Leukopenia generally developed on the first to the fourth day after the first inhalation and continued for 3 to 5 days. In a considerable number of cases the intensity of

leukopenia was parallel with the development of the objective and subjective symptoms of illness. Only rarely was leukopenia the sole symptom pointing to an interaction between the virus and the human organism. Usually it was accompanied by other clinical manifestations. It should be emphasized that, in those patients showing distinct leukopenia, an especially pronounced increase in specific virus-neutralizing antibodies was observed. The white cell picture of volunteers with leukopenia was characterized (in absolute values) by neutropenia, lymphopenia, eosinopenia and monocytosis.

Thus the blood picture of many of the persons inoculated with the influenza virus conformed exactly with that described for epidemic influenza (Rütimeyer, Naegeli).

From the data of one of us (A.A.K.) obtained during the 1936 epidemic in Leningrad, leukopenia was a most constant finding in uncomplicated epidemic influenza. It was observed particularly often on the second or third day of illness, when it was extremely pronounced (up to 3000 per c.mm.). In approximately 20% of the patients with uncomplicated epidemic influenza leukopenia was preceded by leukocytosis lasting for one day. After the fourth day of illness the leukopenia became less distinct, and on the 10th or 11th day the leukocyte count returned to normal. The leukocytic picture of uncomplicated epidemic influenza showed the following changes:

1. Lymphopenia on the first 2 days of illness, disappearing by the 5th day and changing during the next few days into a pronounced lymphocytosis.
2. Neutropenia, most distinct by the 5th day of illness, and returning to normal in 8 to 12 days.
3. Eosinopenia, or a complete disappearance of eosinophils.
4. Monocytosis in a considerable number of patients, especially during the first 2 days. The monocytes in the majority of cases were atypical and in structure of the nucleus and protoplasm resembled histiocytes.

Minor differences between the blood pictures of experimentally infected volunteers and naturally-occurring cases of influenza consisted mainly in a less extreme leukopenia and an absence of toxic and degenerative alterations in the neutrophils in the experimental cases.

In the cases of 12 of the 72 volunteers the white cell count increased after inhalation of the virus. All volunteers of this group either had infective foci before inhalation (chronic inflammation of the accessory sinuses of the nose, chronic purulent otitis, abscesses on the fingers, etc.) or suffered some other complication after inoculation (angina, pneumonia, localized bronchitis, gumboil, etc.).

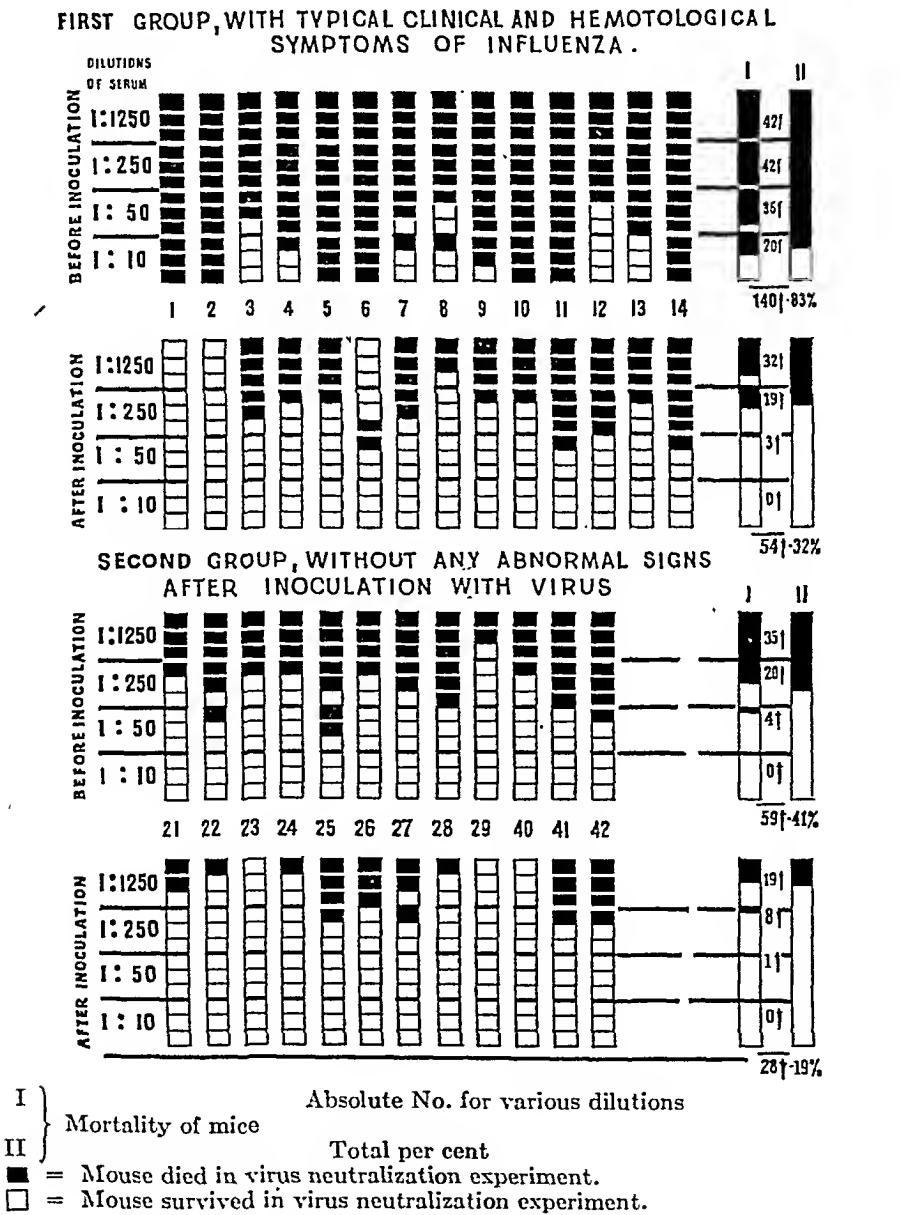
In the remaining 35 volunteers inhalation of the virus had no noticeable effect on the leukocyte count.

Immunologic Changes in the Blood of Inoculated Volunteers. *Method for the Quantitative Titration of Protective Antibodies.* In the majority of cases blood was drawn both before inoculation, and again 10 to 15 days after inoculation, from each volunteer. Titrations of the virus-neutralizing

antibody content of both serum samples from each patient were conducted simultaneously. Samples of various dilutions of the serum were mixed with equal amounts of a suspension of the Leningrad virus. The final dilutions of the serum were 1 in 10, 1 in 50, 1 in 250 and 1 in 1250. The quantity of virus used was 0.05 cc. of a 1 in 400 dilution, corresponding to 100 to 250 MLD for mice. After 30 minutes' contact at room temperature each serum-virus mixture was introduced intranasally into 3 mice under ether anesthesia. All the mice succumbing after 5 to 10 days were autopsied, and death was considered due to virus infection only in those cases in which the lungs showed complete hepatization and contained but few bacteria.

CHART III.

CONTENT OF VIRULICIDAL ANTIBODIES IN THE BLOOD OF HUMAN VOLUNTEERS.



The results of the investigation are given in Chart III. The virus-neutralizing antibody content of each serum is represented in the form of columns consisting of 12 squares divided into 4 groups, depending upon the dilution of the serum. Each black square represents the death of a mouse, and each white square its survival. The data in the upper portion of the table (First group) was derived from 14 volunteers who developed clinically typical influenza with leukopenia following inoculation with influenza virus. The data in the lower portion of the table (Second group) represents the findings in the cases of 12 volunteers who exhibited no clinical evidence of influenzal infection as a result of inoculation with the virus.

The results of the immunologic study indicate, first of all, that the development of the experimental disease by inoculated volunteers is closely dependent upon the quantity of specific antibodies in their blood before inoculation. Thus, in the group which showed distinct symptoms of influenza following inoculation, the concentration of protective antibodies in the blood before inoculation was extremely low; in a considerable number of these even the lowest dilution of serum failed to neutralize 100 lethal mouse doses of virus. On the other hand, the blood sera of the majority of the volunteers in the second group, who proved resistant to large doses of the mouse virus, showed a high content of specific antibodies even before inoculation. Serum dilutions of 1 in 10 in all cases, and dilutions of 1 in 50 in a majority of cases (and some dilutions of 1 in 250) neutralized the dose of virus employed in the mouse protection tests.

To summarize the neutralization experiments with sera obtained from volunteers prior to inoculation, 146 of 168 mice (87%) receiving mixtures of virus and sera from susceptible persons (First group) died, while of 144 mice injected with virus and sera from non-susceptible volunteers only 59 (41%) died.

A second fact, clearly shown by the data in Chart III, was that the virus-neutralizing antibody content of the sera of the majority of the volunteers was markedly increased following inoculation with influenza virus. This was especially true in the first group, showing clinical symptoms, and here 25 to 100-fold increases in the antibody titer were usual. In isolated cases (Nos. 1, 2, 4) the quantity of antibodies after 2 or 3 inhalations of the virus reached exceptionally high values: a serum dilution of 1 in 1250 still neutralizing 100 MLD for mice of the virus. A distinct and consistent increase in the neutralizing antibodies in the sera of volunteers of the second group (resistant) after inoculation with influenza virus was also observed, though here the increase was less pronounced than that found in the first group. It is probable that in immune individuals the virus is too rapidly destroyed upon introduction into the respiratory tract to elicit a maximal immunity response.

These data permit one to conclude that inhalation of influenza virus, attenuated by protracted passage through ferrets and mice,

may be worthy of attention as a means of increasing the quantity of protective antibodies in human beings and perhaps also of enhancing their resistance to a subsequent influenza infection. We are now accumulating information on the duration and intensity of the specific alterations in the blood of those subjected to inoculation, as well as developing methods for the active immunization of humans by means of inhalation of the virus.

We should like to emphasize that the results of these immunologic studies obtained in human volunteers experimentally infected with the passaged influenza virus conform completely with the observations on uncomplicated influenza made during the time of the recent outbreak in Leningrad (1936). At that time we determined that there was a regular and sharp increase in the concentration of specific antibodies in the blood of influenza convalescents. We demonstrated that, while the majority of investigated sera obtained from influenza patients during the acute stage of their disease failed to neutralize virus even in 1 in 10 dilutions, the sera of patients after convalescence were active in dilutions of 1 in 250 and in rare cases even in dilutions of 1 in 1000. In other words, the concentration of influenza virus-neutralizing antibodies was increased 25 to 100-fold following an attack of influenza.

Fate of the Inhaled Virus. The period of time during which influenza virus persists on the upper respiratory tract mucosa of inoculated volunteers has been studied. In these experiments throat washings, obtained from volunteers at various intervals after inhalation, were tested for virus by mouse inoculation.

Method. Various dilutions of the throat washings (1 to 1, 1 to 10, etc. to 1 to 100,000) were introduced intranasally into white mice, three mice being used to test each dilution. After 6 days the mice which survived were killed and a 10% suspension of their lungs was used for the inoculation of fresh mice. If the latter died of virus infection, it was concluded that the virus was present in the given dilution. The results of one of the experiments in this series are given in Table 1.

TABLE 1.—DILUTIONS OF THE THROAT WASHINGS OF 3 VOLUNTEERS INOCULATED BY A 30-MINUTE INHALATION OF THE VIRUS.

	1:1	10 ⁻¹	10 ⁻²	10 ⁻³	10 ⁻⁴	10 ⁻⁵
Immediately after inoculation . . .	+	+	+	+	+	—
After 4 hours	+	+	+	—	—	—
After 24 hours	+	+	—	—	—	—
After 48 hours	+	+	—	—	—	—
After 72 hours	—	—	—	—	—	—
+ = Influenza virus present. — = Influenza virus absent.						

As shown in the table, the rather high concentration of virus immediately after inoculation diminished markedly within 24 to 48 hours. It seems highly probable that the virus used to inoculate the volunteers had lost much of its original virulence for man as a result of its repeated passage through ferrets and mice.

This rapid disappearance of the virus from the inoculated volun-

teers definitely agreed with the data of the immunologic studies upon the experimental cases. The higher the content of specific antibodies in the blood before inoculation the more rapid was the disappearance of the introduced virus. And, inversely, the longest persistence of the virus was observed in those volunteers having a low level of protective antibodies.

The low virulence of the passaged strain of the influenza virus may also account for the failure of the experimental disease to spread by contact to the surrounding personnel. This point, however, requires additional confirmation through observations on people more fully susceptible to influenza, inasmuch as the present investigation was carried out immediately after the end of the 1936 epidemic in Leningrad.

The Effect of Inhalation of the Virus on the Bacterial Flora of the Throat. Bacteriologic investigations carried out on patients with uncomplicated epidemic influenza at the time of the last outbreak in Leningrad disclosed large numbers of pneumococci, Pfeiffer's bacilli, catarrhal micrococci, and in many cases, also hemolytic streptococci in the throats of 32 patients during the first few days of illness. The highest concentration of these bacterial invaders was reached in the first 5 to 6 days. After convalescence (10 to 15 days after the onset of the disease) the average number of these microorganisms fell to a value one-thousandth or less of that observed during the first few days of illness. This suggested that the primary infective agent in epidemic influenza—probably a filtrable virus—lowers the resistance of the respiratory tract to such an extent as to permit the widespread multiplication of bacteria like the pneumococcus or Pfeiffer's bacillus. In consequence, there may be formed in the nose and throat a great reservoir of infective organisms, which play a decisive rôle in the development of the various complications of influenza.

It seemed of considerable interest to determine whether such an activation of the secondary microorganisms took place in the cases of human beings experimentally inoculated with the virus. Repeated bacteriologic examinations of 48 volunteers before inoculation and on various days after inhalation of the virus, however, failed to reveal any quantitative or qualitative changes in the bacterial flora of the upper respiratory tract in response to the introduction of the virus. Even in the volunteers who reacted to inhalation with a whole series of symptoms very similar clinically to naturally-occurring influenza did we fail to observe a distinct activation of pneumococci, hemolytic streptococci, Pfeiffer's bacilli or catarrhal micrococci. This was true even in the cases in which these bacteria were present before inoculation. The failure to note distinct activation of the bacterial flora of the upper respiratory tract in the infected volunteers may have been due either to the quality of the virus used in inducing the infections (passage of the virus in animals may have attenuated it for man) or to the low virulence of the

bacteria naturally vegetating in the upper respiratory tracts of most healthy people.

On the basis of our experiments, we may conclude that the inhalation of large doses of influenza virus is relatively harmless since our volunteers showed either no distinct reactions or symptoms of only a mild influenza. These findings make it highly worthwhile to study further the possibilities of the use of inhaled influenza virus as a means of actively immunizing people against epidemic influenza.

Summary. 1. About 20% of the 72 volunteers to whom large doses of the Leningrad virus or the WS virus of Smith, Andrewes and Laidlaw were administered by inhalation showed a series of clinical and hematologic changes conforming with the main findings in mild influenza. Considering the fact that only some of the volunteers became ill and these with but a light form of influenza, it is evident that the inhalation even of large doses of the virus previously adapted to ferrets and mice is relatively harmless for humans.

2. The development of the experimental illness was found to be closely related to the quantity of specific protective antibodies contained in the blood of the volunteers inoculated with the virus. All cases showing clinical symptoms typical of influenza had a low value of virucidal substances before inoculation. The majority of volunteers not reacting to the introduction of the virus showed large quantities of specific antibodies even before inhalation.

3. A considerable number of the inoculated individuals reacted to inhalation of the virus with an increase in the quantity of neutralizing antibodies in the blood. An especially large increase in the concentration of these virucidal substances (25 to 100 times) was noted in those volunteers showing the clinical symptoms of influenza. It is evident from this that inhalation by humans of the virus attenuated by passage through ferrets and mice, is worthy of study as a method for decreasing the susceptibility of people to influenza infection.*

4. Virus which has been adapted to the ferret and the mouse appears to have lost thereby its original virulence for man and to be incapable of further multiplication in the human organism. This was indicated by our observation that the influenza virus, introduced into the individual in the form of a suspension of the lungs of diseased mice, did not multiply in the mucosa of the respiratory tract

* The suggestion that influenza virus be administered by inhalation as a prophylactic measure against epidemic influenza seems, for the present at least, a heroic recommendation. Our knowledge concerning the properties and activities of the virus is as yet incomplete, we know nothing concerning its possible fluctuations in virulence, and the complications to which it may give rise are unpredictable. Influenza is a notoriously variable and protean disease and until we have some understanding of why, even in a given epidemic, it may manifest itself as an extremely mild illness in one individual and a rapidly deadly ailment in another, any method of immunization dependent upon actual infection, even with an apparently attenuated strain of virus, must be viewed yet as purely an experimental procedure and not applicable to widespread and general use.—EDITOR.

and died off during the course of the first few hours after inoculation. It was also shown that an activation of the potentially pathogenic microorganisms (Pfeiffer's bacillus, the pneumococcus, and the hemolytic streptococcus), so common in cases of genuine epidemic influenza, did not occur in individuals inoculated by inhalation with large doses of the animal-passaged influenza virus.

We are deeply indebted to Dr. Richard E. Shope for his interest in our work and his kind assistance in revising the manuscript.

BIBLIOGRAPHY.

- (1.) Andrewes, C. H., Laidlaw, P. P., and Smith, W.: *Brit. J. Exp. Path.*, 16, 500, 1935. (2.) Smorodintseff, A. A., Drobyshevskaya, A. I., and Shishkina, O. I.: *Lancet*, 2, 1383, 1936. (3.) Smorodintseff, A. A., Drobyshevskaya, A. I., Ostrovskaya, S. M., and Shishkina, O. I.: *Ibid.*, p. 1381.

VALUE OF FEVER THERAPY IN THE ARTHRITIDES.*

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SINCE the foundation, in November, 1934, of the University of Nebraska Fever Therapy Research Department, now located at the Bishop Clarkson Memorial Hospital in Omaha, we have treated 172 arthritic patients, of whom this report covers 81 cases. This department uses for the induction and maintenance of fever three Kettering hypertherms† operated by a corps of specially trained nurses.

Each patient is carefully examined before treatment to determine eligibility and tolerance for fever therapy, one requisite being that the patient must be a good surgical risk before submitting him to the high fever, 106 to 107° F., necessary in the treatment of gonorrheal arthritis. The lower fevers, 103 to 104.5° F., used in the treatment of the other forms of arthritis, fortunately do not require such strict limitations. A careful history, complete physical examination with special emphasis upon locating focal infections, Roentgen rays of the sinuses, and of at least one of the affected joints, blood Wassermann test, blood sedimentation rate, complete blood count, and urinalysis are done on each case in order properly to diagnose and classify the type of arthritis.

All cases are under the supervision of an Arthritis Committee‡ which consists of four internists, an oto-laryngologist, an ortho-

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† We are indebted to Dr. Charles F. Kettering, Director of General Motors Research Department, and Dr. Walter M. Simpson, Director of the Kettering Institute for Medical Research, Miami Valley Hospital, Dayton, Ohio, for the loan of the Kettering Hypertherms used in our studies.

‡ F. Lowell Dunn, M.D., Chairman; Lynn T. Hall, M.D., F. W. Niehaus, M.D., and E. E. Simmons, M.D., Internists; Delbert K. Judd, M.D., Oto-laryngologist; Herman F. Johnson, M.D., Orthopedist; F. Lowell Dunn, M.D., Clinical Pathologist.

pedist, a roentgenologist, and a clinical pathologist. Various members of this committee carefully study each case and utilize all rational types of therapy for the various arthritides, but are primarily interested in evaluating the rôle of fever therapy in these diseases.

Acute Rheumatic Fever. The excellent results obtained by fever therapy in the treatment of chorea interested us to try the same treatment in that most serious and incapacitating illness of the acute rheumatic fever triad, namely, acute rheumatic endocarditis; and to study our chorea patients carefully for evidence of complicating rheumatic endocarditis.

To date we have treated 9 cases of acute rheumatic fever with endocarditis and have also observed the results of fever therapy in 3 cases of chorea, which started primarily as rheumatic endocarditis, later developing typical chorea. The duration of the active state of acute rheumatic fever in these 12 cases ranged from 1 week to 9 months. All had active rheumatic endocarditis, with clinical findings of valvular heart disease, fever, and laboratory evidence of activity, and 1 had complicating rheumatic pericarditis. The patients' ages ranged from 7 to 40 years.

The treatment of cases of acute rheumatic fever consists of maintaining a fever of 103 to 105° F., depending on the response of the patient, for a period of 2½ to 4 hours. We feel that prolonged treatments of higher fevers are not well tolerated by these cases. The treatments are repeated every 3 or 4 days until the disease is improved or becomes inactive.

Following is the report of a typical case with a good result:

CASE 1.—A woman of 40 had rheumatic pains, low-grade fever, marked mitral stenosis in an active stage of endocarditis; and 6 weeks of almost total bed rest, large doses of salicylates, and supportive treatment had failed to improve or relieve fully the pain. She withstood the fever treatments very well, with no apparent heart embarrassment. After 5 treatments her pain was gone, she was free of fever, her leukocyte count was normal, and her sedimentation rate was much lower. She left the hospital at the end of 22 days.

Five similar patients with acute articular rheumatism and active rheumatic endocarditis, after an average of 5 fever treatments, became free of pain and fever and had laboratory findings indicative of a prompt return to the inactive stage of acute rheumatic fever. One of these patients had acute rheumatic pericarditis which, after becoming steadily worse under bed rest and large doses of salicylates, cleared up following 4 fever treatments. He left the hospital 20 days after admission.

The 3 following cases showed moderate improvement but less favorable results than the preceding 6.

CASE 1.—A man, with slight active endocarditis and severe pains previously requiring opiates, left the hospital after two fever treatments with some remaining pains, but free of fever, with normal leukocyte count and

much slower sedimentation rate. When heard from a month later he was entirely free of pain and fever and in good health. His slight pain on dismissal and a tonsillectomy which made it impossible to evaluate the results from the fever therapy classify him in the list of less successful cases.

CASE 2.—A girl of 11 was seen 1 week after an acute exacerbation of acute rheumatic fever, with a moderate degree of mitral stenosis, a fever and rather intense joint pains and became after 3 fever treatments free from pain and fever, with normal laboratory findings. She remained free of symptoms for 2 months and then had a recurrence of fever, acute endocarditis and rheumatic nodules, which required 4 months of bed rest to clear up. Although she responded well to fever therapy, her early relapse proved disappointing. Her case may well have deserved more treatments.

CASE 3.—A girl of 18 with very painful joints, low-grade fever, systolic murmur over apex transmitted to axilla, and incapacitated for 9 months, after 9 fever treatments was improved enough to return to school this fall. She has had moderate relief, more than with any other type of treatment, but not an entire relief of symptoms. A longer subsequent period is necessary in order fairly to evaluate her treatment.

In our group of chorea patients we found 3 cases which had started as acute articular rheumatism with endocarditis, later developing chorea. These patients ran low-grade fever and had the laboratory and auscultatory heart findings of active rheumatic endocarditis. Their ages ranged from 9 to 10 years, and the duration of the disease ranged from 2 weeks to 4 months. All of these patients, following an average of 9 fever treatments, became free of choreic manifestations, fever and pain; and their laboratory findings indicated that they were in an inactive stage of rheumatic fever. One has remained for over 1 year in excellent health and free of all evidence of active rheumatic disease, including the heart murmur.

Thus, in 9 cases of acute rheumatic fever with endocarditis, 6 became inactive in a relatively short period, an average of 24 days. The 3 cases of chorea with rheumatic endocarditis observed became inactive in an average time of 46 days; this longer period was due to treatments, in the beginning of our work, spaced at only weekly intervals. In the series, 75% have become inactive, free from pain and fever after an average of 7 fever treatments. In the remaining 25%, it is possible that additional treatments would have produced more favorable results.

Because of the small number of patients who have come under our observation and the short time that has elapsed since treatment, we cannot form definite conclusions. In rheumatic fever it is especially hard to determine what effect artificial fever has on the great tendency for relapses of activity to occur. We hope in the future to determine whether this type of therapy will prevent such recurrences of activity. But even though some patients may continue to have relapses after artificial fever therapy, we believe it possible, by shortening the duration of each period of activity, to reduce to a minimum the damage to the heart.

In consulting the literature we find reports^{6,11a} on results of artificial fever therapy produced by various vaccines, serums and

foreign proteins in treatment of acute articular rheumatism—with apparently good results. We can find only two reports on the results of artificial fever therapy, mechanically produced, in the treatment of acute rheumatic fever with endocarditis *per se*,^{11b,c} but there are numerous reports on the results in the treatment of chorea.^{3,7,9} Some of these authors comment on the fact that chorea patients with endocarditis tolerate the treatments very well, and that there is no apparent heart damage from fever therapy. Some state that they believe the rheumatic and endocarditic phase may be slightly benefited,⁸ but this feature of the disease, for the most part, has only been casually observed, because observers were primarily interested in the outcome of the chorea. Barnacle, Ewalt and Ebaugh¹ report 13 cases of chorea, 8 of whom had a complicating rheumatic endocarditis. An analysis of their report definitely shows that the rheumatic endocarditis was improved in 6 of the 8 cases.

Conclusion. When we take into consideration the chronic nature of rheumatic fever, the serious heart complications, the lack of any recognized therapy other than prolonged bed rest, supportive measures, and climatic changes, we believe that artificial fever therapy provides sufficient promise to justify further trial. The results obtained in chorea, one phase of this disease, justify this attitude. We feel from our limited observations that the marked relief seen in such a short period of time in 75% of our cases is a great improvement over any other type of therapy now used, and should encourage others to try this type of treatment and report their results.

Gonorrheal Arthritis. Out of 32 cases of gonorrheal arthritis treated in our fever therapy department, we have selected 23 with adequate diagnostic and follow up work from which to draw conclusions. There were 15 males and 8 females, with ages ranging from 19 to 50; the duration of the disease was from 4 days to 1 year.

The fever treatment in these cases consisted of 6 hours of fever of 106 to 107° F., repeated every 3 to 5 days, according to physical condition of the patient; the usual maximum was 25 hours.

Of these 23 cases, 15 (65%) were cured during the time they received treatments. We classify as cured those cases in which there was a complete cessation of pain and an absence of evidence of active inflammation, though not necessarily a complete return to normal function in the affected joints. Several with complete or almost complete ankylosis had only a great improvement of movement in the affected joints, with 50 to 75% of normal range at the end of treatment. Of the 15 cured cases, all of whom had other manifestations of gonorrheal infection, it was possible after fever therapy to get positive urethral smears in only 2. These 2 cases were entirely pain free and had no other evidence, subjective or objective, of their gonorrheal arthritis. There were 4 cases (17%) with marked improvement. Although these patients were greatly

improved, they still had a little pain on motion or a slight degree of swelling in the affected joints. Three cases (13%) received only slight improvement from their treatments. Only 1 case (4%) received practically no benefit, easily attributable to insufficient treatment.

The cases that were cured received an average of 25 hours of fever between 106 and 107° F., those markedly improved received an average of 27.8 hours, the cases with slight improvement received only 8.5 hours, and the unimproved case only 7 hours of this same elevation of fever.

In examining our records, contrary to the experience of others,^{5,10} we were unable to determine any factors that might indicate the type of result to anticipate, with the exception of those cases having exostosis of the os calcis. The duration of the disease in the cured group ranged from 4 days to 7 months, in the markedly improved group from 4 days to 6 months, in the slightly improved group from 2 weeks to 1 year, and in the unimproved case the disease was of only 4 days' duration. There were no definite clinical or laboratory findings that were of benefit in prognosticating the end result other than the cases with spurs of the heel (os calcis), which required more hours of sustained fever to become pain free.

Apparently the only criteria for cure of this type of arthritis are the subjective and objective findings in the affected joints, disregarding positive smears for the gonococcus. Most of the treated cases continued to improve for some weeks after the termination of fever therapy.

Thus, 82% of the cases treated were either cured or markedly improved; the other 18% did not receive enough fever therapy to be of value.

An analysis of all of these findings would indicate that our slightly improved cases and the unimproved case received insufficient fever therapy to get a good result. It would seem that a minimum of 25 hours of fever between 106 and 107° F., the average amount of fever in cured cases, is necessary before drawing adverse conclusions in the individual case. Indeed, when a case difficult to classify is seen, and the patient does not show marked benefit from fever therapy, a more careful examination often discloses that we are dealing with chronic infectious arthritis that also has a focus of gonococcal infection.

Our experience has also shown us that the cases with rather severe deformities require adequate orthopedic measures as well as fever therapy.

Conclusion. It is our belief that artificial fever therapy is the best treatment now available for gonorrheal arthritis. Most patients, unable to move on account of severe pain, are practically free of pain after one session of fever. The greatest advantage is probably the rapidity with which a favorable result is obtained, thus

greatly shortening a disability that usually is quite prolonged, and preventing the development of permanent deformities. When these cases are treated by fever therapy at the onset of the disease, the majority are cured before any deformity results.

Atrophic Arthritis. Since chronic infectious, atrophic, rheumatoid arthritis has been so resistant to treatment, it is natural that we should see more cases of this type in our fever therapy department than of other types of arthritis. Due to the fact that these individuals have tried so many types of therapy without benefit, and because of the extreme discomfort and disability they suffer, they naturally are anxious to try any new type of treatment that may be of benefit. After reading the reports of various observers concerning results in the treatment of this type of arthritis and the small percentage of patients that were benefited,⁴ we concluded that fever therapy in itself would not be of great benefit to this group. We believe atrophic arthritis is a disease of the entire body, of which the joint manifestations are only a part, and that in order to benefit these cases the general condition of the patient is of more importance than any type of treatment directed toward the joints themselves. Most of these patients show evidence of active infection, such as leukocytosis, mild fever and increased sedimentation rate; many show a marked secondary anemia, loss of weight and muscular atrophy—evidence of vasomotor instability and various nervous manifestations. Therefore we have used fever therapy in this group largely as an adjuvant to other types of treatment.

To date we have treated 82 cases of atrophic arthritis with fever therapy in combination with other forms of therapy. Of this group there were only 36 cases with definite diagnostic criteria, plus adequate follow-up data for a period of 6 months or longer; 11 were males and 25 females. Their ages range from 15 to 66 (average 40.7). The duration of the disease was from 4 months to 18 years (average 5.7). There were all types of involvement, the severity of which ranged from simple monoarticular involvement to complete disability. The average number of hours of fever above 103° was 22.4. The results obtained were graded according to clinical results, based on relief of pain, relief of stiffness and relief of swelling and deformity of affected joints. In this group we found our results as follows:

	None.	Slight.	Moderate.	Marked.
Relief of pain	22	11 0	25.0	42
Relief of stiffness . .	22	0	25.0	53
Relief of swelling and deformity	33	19.4	16.6	31

We furthermore tabulated our results under the heading of improvement of general condition, including laboratory as well as clinical data to support this conclusion. The laboratory data included an elevation in the red blood cell count after treatment in those that had showed a moderate or marked anemia, a decrease in

the blood sedimentation rate, the disappearance of febrile reactions and a decrease in the white blood cell count. The clinical good results were evaluated according to the general wellbeing on the part of the patient, a decrease in the amount of disability, and an increase in weight in those who were underweight. We were able to show in these cases an improvement in 78% of all the patients treated.

Practically all of the cases which were treated had formerly availed themselves of all the ordinarily accepted types of therapy, such as rest, internal medication, vaccines, visits to hot springs, massage, diathermy, and various other types of therapy. In all the cases seen in our department, after careful examination and Roentgen ray studies, 81% of these cases had already had all demonstrable foci of infection eradicated.

The adjuvant treatment consisted of iron or liver therapy or both, for those with anemia, some form of salicylates to relieve pain, high vitamin and high caloric diets for those patients who were underweight, limited diets with an attempt to reduce weight in those that were overweight, the administration of various vitamins in the form of cod liver oil, viosterol, yeast tablets or concentrates of A, B, and D vitamins. A small group of patients were put on large doses of vitamin D, *i. e.*, up to 200,000 units a day, and the fever treatments were given in groups. Four to 6 treatments at 103 to 104.5° F. were given at 5 to 7-day intervals. Following a rest period of 6 to 10 weeks, patients were given another group of fever therapy treatments if unimproved.

Of the cases that were treated by fever therapy the percentage of those with severe deformities was very high, and we soon learned that one of the most important treatments in this type of disease was the correction by orthopedic measures of existing deformities; and the prevention of deformities in those cases that had none. We feel that this phase is one of the most important in the treatment of this type of arthritis. We also found that daily massage of the atrophied muscles was very essential and very helpful. The best results were obtained in those cases which presented themselves in the poorest physical condition; that is, cases with marked anemia and extreme underweight showed very marked improvement from treatment of anemia and increasing the weight by dietary measures and the use of insulin. By improving the general condition of the patients, we also improved their ability to tolerate the discomforts of this disease.

Conclusion. We feel that artificial fever therapy is of considerable value as an adjuvant in the treatment of chronic atrophic arthritis; that it decreases general disability and swelling of the affected joints in a large percentage of cases; but that it is only an adjuvant and that the prime consideration in all cases is the additional treatment of the patients' general condition, together with proper orthopedic supervision and correction when necessary. In order ultimately

to evaluate the rôle of fever therapy, a larger number of patients must be studied over a much longer period of time than has been possible thus far.

Hypertrophic Arthritis. If we accept that hypertrophic arthritis is a degenerative rather than an infectious disease due to advancing age and strain on affected joints from overweight, occupation, trauma and like factors, it is not surprising that our results with artificial fever therapy are the most unfavorable of any of the arthritides. At present, 10 cases treated in our fever therapy department have sufficient diagnostic and follow-up data to report—6 males and 4 females, the ages ranging from 38 to 75 years, and the duration of the disease from 1 to 30 years.

The results reported in the literature by other groups were so devoid of promise^{2,4} that all these patients were treated only after being advised of the very doubtful prospects of any permanent benefit. These cases were given treatments of fever of 103 to 105° F., the length of the treatment being 3 to 4 hours. Of this group 5 cases (50%) were not benefited; 1 (10%) was markedly improved; 2 (20%) were moderately improved; and 2 (20%) were slightly improved. These figures represent the results some months after stopping fever therapy. Practically all cases were improved directly after the treatments, but this improvement was only transitory and the pains returned in a few days or a week.

Conclusion. We think that fever therapy is of very little value in the usual uncomplicated case of hypertrophic arthritis. We believe, however, that those cases of hypertrophic arthritis aggravated by superimposed trauma or infection are quite often benefited by fever therapy.

Summary. 1. Of 9 cases of acute rheumatic fever with active endocarditis, 6 became inactive in an average of 24 days, following an average of 5 fever treatments. Three cases of acute rheumatic fever with active endocarditis and complicated by chorea became inactive in an average of 46 days, following an average of 9 fever treatments. We think this is a marked improvement over any other type of therapy now used and justifies further investigation of this method of treatment.

2. Of 23 cases of gonorrheal arthritis, 82% were cured or markedly improved after an average of 26.4 hours of fever maintained between 106 and 107° F. We believe that a minimum of at least 25 hours of fever of this elevation is necessary before concluding this therapy is a failure. It is the best type of therapy known to date, and should be instituted early. Orthopedic measures may be necessary.

3. We believe artificial fever therapy is a valuable adjuvant, along with dietary, supportive, and orthopedic measures, in the treatment of atrophic arthritis. This combination of treatment was of benefit in 78% of patients treated.

4. Hypertrophic arthritis is benefited by artificial fever therapy only in those cases where there is a superimposed traumatic and infectious element.

5. In any type of arthritis, with or without an infectious element, we think that heat, the oldest known and most universally applied type of therapy, is a justifiable therapeutic measure. Other means of producing febrile reactions are not so efficiently controlled nor so safe, in our opinion, as mechanically induced fever therapy. The beneficial effects of fever therapy in the arthritides, with the possible exception of gonorrheal arthritis, are in all probability not solely bactericidal, but rather the result of the beneficial effects of vasodilatation and increased immunologic response.

6. Artificial fever therapy should be given only by physicians and nurses who have received adequate preliminary training. Such treatment is not adaptable to office practice.

REFERENCES.

- (1.) Barnacle, C. H., Ewalt, J. R., and Ebaugh, F. G.: *J. Am. Med. Assn.*, 106, 2046, 1936. (2.) Desjardins, A. U.: *Arch. Phys. Ther.*, 17, 206, 1936. (3.) Desjardins, A. U., and Popp, W. C.: *Our Experience with Fever Therapy*, Trans. Fifth Ann. Fever Conf., Dayton, Ohio, p. 7, 1935. (4.) Hench, P. S., Slocumb, C. H., and Popp, W. C.: *J. Am. Med. Assn.*, 104, 1779, 1935. (5.) Kendall, H. W., Webb, W. W., and Simpson, W. M.: *Am. J. Surg.*, 29, 428, 1935. (6.) Menzer, A.: *Med. Klin.*, 18, 1022, 1922. (7.) Metz, M. H.: *J. Am. Med. Assn.*, 106, 1658, 1936. (8.) Neyman, C. A., Blatt, M. L., and Osborne, S. L.: *Ibid.*, 107, 938, 1936. (9.) Schnabel, T. G., and Fetter, F.: *Ann. Int. Med.*, 9, 398, 1935. (10.) Stecher, R. M., and Solomon, W. M.: *AM. J. MED. SCI.*, 192, 497, 1936. (11.) Sutton, L. P., and Dodge, K. G.: (a) *J. Pediat.*, 3, 813, 1933; (b) 6, 494, 1935; (c) *J. Lab. and Clin. Med.*, 21, 619, 1936.

STUDIES IN SYPHILITIC CARDIOVASCULAR DISEASE.

I. UNCOMPLICATED SYPHILITIC AORTITIS: AN ASYMPTOMATIC CONDITION.

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THERE are few conditions in which early diagnosis is of greater importance than in syphilitic involvement of the cardiovascular system. The accomplishments of recent years that have been made in the specific treatment of syphilis, and especially in the technique of the therapeutic management of its cardiovascular complications, have rendered prompt institution of proper treatment of even greater moment than heretofore. The predilection of syphilis for the cardiovascular system, its distribution through vascular channels, and the premature and tragic consequences of syphilitic cardiovascular disease have long been known. Only recently, however, have adequate therapeutic methods been available, sufficiently effective in their results to outweigh the dangers inherent in their use. Because

so much depends upon the stage of the disease in which treatment is begun, it is therefore of paramount importance that the diagnosis be established before any complications have arisen; that is, while the pathologic process is still one of an uncomplicated syphilitic aortitis.

The recognition of syphilitic aortitis as a progressive pathologic process is necessary before its uncomplicated stage can be defined. Simple invasion of the aorta by the *Treponema pallidum* is possibly universal in all untreated syphilitics. Actual demonstrable involvement, gross or microscopic, has been found in a large percentage of syphilitic subjects coming to necropsy, Warthin⁶ reporting 90% in 490 postmortem examinations, and Langer³ maintaining that from 70% to 80% of adult syphilitics show evidence of such involvement. From the stage of barely demonstrable involvement, gradual progression may take place until the aortic valves are so distorted as to produce regurgitation; or the syphilitic aortitis may result in weakening of the wall of the aorta with dilatation and aneurysm formation; or the proliferative process may so encroach upon the ostia of the coronary vessels that the circulation to the heart muscle is impaired. If, however, none of these three possibilities has occurred, and if the pathologic process is limited in its distribution to the aortic wall, the condition may then be regarded as an uncomplicated syphilitic aortitis.

Recently, the various symptoms and physical signs ascribed to syphilitic aortitis have been reviewed by Moore, Danglade and Reisinger⁵ in a study of the clinical records of patients in whom the diagnosis was established at autopsy. They have tabulated, in order of relative importance, the following criteria for the diagnosis of uncomplicated syphilitic aortitis: 1, Teleroentgenographic and fluoroscopic evidence of aortic dilatation; 2, a tympanitic, bell-like, tambour accentuation of the aortic second sound; 3, a history of circulatory embarrassment; 4, increased retromanubrial dullness; 5, progressive cardiac failure; 6, substernal pain; 7, paroxysmal dyspnea. They further suggest that the presence of 3 or more of these symptoms and signs in a young adult syphilitic patient without mitral disease or hypertension is strong evidence for the diagnosis of uncomplicated syphilitic aortitis. These diagnostic criteria have been adopted by the Coöperative Clinical Group now engaged in the study of the treatment of syphilis, and are reported by Cole and Usilton¹ as those on which the diagnosis of uncomplicated syphilitic aortitis has been made in their patients.

The physical signs enumerated above are incontestably those of syphilitic disease of the aorta and are all dependent upon aortic dilatation. On the other hand, the so-called characteristic symptoms of syphilitic aortitis are by no means indisputable and the validity of ascribing certain of these symptoms to a purely uncomplicated aortitis has been seriously questioned. Keefer and Resnik,² in a

review of the clinical and necropsy records from the medical clinic of the Johns Hopkins Hospital, found that in 24 cases of uncomplicated syphilitic aortitis, not one had shown dyspnea on exertion, paroxysmal dyspnea or signs of myocardial insufficiency. Every case of aortitis in which one or more of these symptoms were found had some additional factor to which the symptom was due—aortic insufficiency, aneurysm, myocarditis, hypertensive cardiovascular disease, or an organic obstructive lesion. More recently, in a study of 346 cases from the Brooklyn Hospital, Maynard and his associates⁴ conclude that myocardial failure appears only after the development of complications and that it is not due to an uncomplicated aortitis. While these symptoms—the story of circulatory embarrassment, progressive heart failure, substernal pain, and paroxysmal dyspnea—have long been regarded as typical of syphilitic disease of the aorta and are to be found in the usual description of the condition, adequate explanation for them has not been advanced and reasonable physiologic mechanisms on which they might depend have not been suggested. A study of the symptoms of uncomplicated syphilitic aortitis therefore seems warranted in order to ascertain whether they depend on the aortic disease *per se* or upon other factors.

Material and Methods. During the past 9½ years, postmortem examinations have been carried out on 1619 patients from the Roper Hospital. This period has been chosen for study merely for the reason that adequate pathologic records are not available for autopsies performed previous to 1927. Of this number, gross or microscopic evidence of syphilitic involvement of the aorta has been found in 211 cases (13%). The clinical and pathologic records of these patients form the basis of the present study. Three complications of syphilitic aortitis have been recognized: 1, deformity of the aortic valves with regurgitation; 2, thoracic aneurysm; 3, narrowing of the ostia of one or both of the coronary arteries by the specific process. The remaining cases have all been considered as uncomplicated syphilitic aortitis. The incidence of the various symptoms in these different groups is shown in Table 1.

TABLE 1.—INCIDENCE OF SYMPTOMS IN SYPHILITIC AORTITIS.

	Total cases.*	Dyspnea on exertion.	Paroxysmal dyspnea.	Precordial pain.	Congestive heart failure.
With aortic insufficiency	49	49	14	10	49
With thoracic aneurysm	31	24	5	7	13
With narrowing of coronary ostia	21	20	5	8	15
Uncomplicated syphilitic aortitis	106	44	4	5	31
Inadequate history	17				

* Thirteen patients had more than one of the complications of syphilitic aortitis, i. e., aortic insufficiency, aneurysm, or coronary involvement.

In evaluating the symptoms of uncomplicated syphilitic aortitis, it is first necessary to distinguish between those cases in which the condition occurs alone and those in which it is associated with other

cardiovascular disease or with lesions which might give rise to a similar symptomatology. Myocardial insufficiency or congestive heart failure from any cause is characterized by dyspnea and evidence of circulatory embarrassment; in those conditions in which the greater strain has been thrown on the left ventricle, paroxysmal dyspnea is not infrequently present. Similarly, tracheal or bronchial obstruction by any intrathoracic tumor, or interference by pressure with the return flow of blood to the right atrium of the heart, will cause like symptoms. Because of this, it is essential further to subdivide the group of cases of uncomplicated syphilitic aortitis to show whether or not other such associated conditions were present. Symptom analysis of the cases in these groups are summarized in Table 2.

TABLE 2.—ANALYSIS OF SYMPTOMS IN CONDITIONS ASSOCIATED WITH UNCOMPLICATED SYPHILITIC AORTITIS.

	Total cases.	Dyspnea on exertion.	Paroxysmal dyspnea.	Precordial pain.	Congestive heart failure.
Hypertensive heart disease	29	29	2	4	28
Chronic nephritis	7	5	1	0	3
Coronary heart disease	5	5	1	1	1
Chronic myocardial degeneration	2	1	0	0	0
Tuberculous pericarditis	1	1	0	0	1
Obstructive lesions	2	2	0	0	1
Without other cardiovascular disease	60	1	0	0	0
Totals	106	44	4	5	34

Comment. Table 2 requires but little comment. The 2 cases classed as chronic myocardial degeneration were probably the end-result of hypertensive cardiovascular disease, although none of the blood-pressure readings obtained during life were elevated. In all of the hypertensive cases both clinical observation and pathologic findings were indicative of the diagnosis. The 7 cases of chronic nephritis were all hypertensive and showed secondary cardiac involvement. The 2 cases with obstructive lesions, one a carcinoma of the larynx and the other a gumma of the neck, both died as a result of respiratory embarrassment. In the group with coronary artery disease 1 case of thrombosis is included, the others merely having had arteriosclerotic changes in the vessel walls, with secondary myocardial damage.

The symptoms under discussion are readily seen to occur, but wherever they are present another reasonable cause for their occurrence is at hand. These are all symptoms of circulatory insufficiency, and where definite myocardial disease is present, it is more logical to believe that the latter is responsible, rather than the mere presence of pathologic changes in the aorta. Only 1 case of simple syphilitic aortitis was observed in which any of these symptoms were present where it could not be explained on the basis of

other cardiovascular disease or an organic obstructive lesion. The lone exception was a case of acute leukemia, and it seems reasonable to assume that the dyspnea on exertion from which this patient suffered was due to his anemia. In every other instance in which any of these symptoms were observed, coexisting disease was found at autopsy which offered an explanation more logical than the mere presence of syphilitic aortitis.

The following case abstracts illustrate the type of case encountered in this series:

CASE 1.—A 55-year-old negro man gave a story of gradually increasing weakness, headache, and dizziness for 1 year prior to his admission to the hospital. Three days before entry, he had a generalized convulsion. There had been no symptoms referable to the cardiovascular system. Examination showed some arteriosclerosis; blood pressure 120/70; heart normal in size, with some supracardiac widening. The blood Wassermann reaction was positive, the spinal fluid examination negative. Convulsions returned, fever appeared, the lungs filled, and the patient died 1 week after entry. Autopsy showed a chronic encephalitis, possibly syphilitic in origin, and bronchopneumonia. The heart was not enlarged. The aorta was widely dilated, its walls thin and inelastic, with scarring typical of syphilitic aortitis.

CASE 2.—A 28-year-old negro man had had a right inguinal hernia for about 1 year when it became incarcerated and irreducible. He had no other symptoms. Physical examination was not remarkable except for moderate widening of the area of retromanubrial dullness. After operation the patient developed a constant fever, 100 to 103° daily. Roentgen ray of the chest showed a widened aorta and some indefinite clouding at the base of the left lung. Three weeks after operation the patient died. Autopsy revealed tuberculosis of the retroperitoneal lymph glands, and miliary tuberculosis of the lungs, liver and spleen. The heart was normal on both gross and histologic examination. The aorta was dilated and considerably scarred, microscopically showing lesions typical of syphilitic involvement.

CASE 3.—A 55-year-old negro man gave a history of illness for 1 month with chills, fever, sweats, and severe headache. There were no cardiac symptoms. Physical examination was negative except for generalized glandular enlargement and a positive Romberg sign. The spinal fluid contained 164 cells, largely lymphocytes, a normal amount of sugar, and gave a positive Wassermann reaction with 1 cc. The patient's symptoms were relieved by lumbar puncture, and repeated spinal taps showed an essentially similar fluid. Terminal bronchopneumonia was the immediate cause of death 2 weeks after entry. Pathologic diagnosis at autopsy included: chronic pulmonary tuberculosis; acute lobular pneumonia; acute miliary tuberculosis of the liver, spleen, kidneys and lymph glands; tuberculous meningitis. The aorta was dilated and scarred, with microscopic lesions typical of syphilitic involvement.

In the 2 cases presented below, cardiovascular disease other than syphilitic aortitis was found at autopsy which would account for the patient's symptoms:

CASE 4.—A 30-year-old negro man entered the hospital with a story of intermittent attacks of pain in the left abdomen and back for 2 months, with the subsequent appearance of hematuria, dysuria, polyuria, loss of weight, and hiccough. There had been some dyspnea on exertion for 2 months, and vague chest pain for 2 weeks. Examination showed nothing of note except a blood pressure of 87/64. Roentgen ray of the chest was normal. The blood urea nitrogen was 181. Because the urine was thought

to be contaminated with feces and because intestinal obstruction was suspected, abdominal exploration was decided upon, and the patient died on the operating table. At autopsy, pyelonephritis and bronchopneumonia were found. There was marked fibrosis of the heart, without enlargement. The wall of the aorta was thick, rough and scarred and microscopic study corroborated the diagnosis of syphilitic aortitis.

CASE 5.—A 49-year-old negro woman gave a story of swelling of the ankles and dyspnea on exertion of 1 year's duration, cough, palpitation, and precordial pain. On examination the heart showed no abnormalities. Blood pressure was 108/62. There was some fluid accumulation at the base of both pleural cavities, which was shown by Roentgen ray, the latter revealing also some cardiac enlargement and aortic widening. The edema disappeared on rest but later returned, and the patient eventually died of heart failure. A guinea pig, inoculated with chest fluid, developed no tuberculous lesions. Autopsy showed tuberculous pericarditis, with considerable enlargement of the heart and complete obliteration of the pericardial cavity. The aorta was scarred with lesions typical of syphilitic aortitis and was moderately dilated.

Analysis of a group of these cases from a slightly different point of view gives a significant result. There were 11 known syphilitic patients who suffered from 1 or more of the symptoms under discussion, who had no evidence of hypertension, mitral disease, or either of the clinically demonstrable complications of syphilitic aortitis—thoracic aneurysm or aortic insufficiency. All of these patients had dyspnea on exertion, 1 had paroxysmal dyspnea, 3 gave a definite history of precordial pain, and 3 were seen with congestive heart failure. Widening of the area of supracardiac dullness was noted in 7 cases, and in each of the 3 patients examined by Roentgen ray, aortic dilatation was found. On the basis of the previously mentioned diagnostic criteria,⁵ the symptoms of all of these cases might have suggested the diagnosis of syphilitic aortitis, particularly in those in which evidence of aortic dilatation was found. However, in addition to the syphilitic aortitis, in every instance coronary artery disease was demonstrated at autopsy, 6 patients showing syphilitic involvement with partial or complete occlusion of one or both of the coronary ostia, and the remaining 5 cases showing coronary sclerosis. Here again, it is more reasonable to ascribe the symptoms to the coronary disease with its attending myocardial involvement, than to aortic disease.

Brief summaries of 2 of these cases are presented herewith:

CASE 6.—A 24-year-old negro man entered the hospital with a story of severe and rapidly increasing dyspnea of 1 month's duration, edema for 3 weeks, sleeplessness, and aching precordial pain. The blood pressure was 130/60. The heart was slightly enlarged, with an apical systolic murmur. Râles at the bases of the lungs, an enlarged liver, and general edema were other positive physical findings. A Roentgen ray showed generalized enlargement of the heart and aorta. Electrocardiogram interpretation revealed right axis deviation. The patient did not improve and died 2 weeks after entry. Autopsy showed considerable enlargement of the heart, especially of the left ventricle, and dilatation of the right. There was no demonstrable insufficiency of the aortic valves, but the valves were thick-

ened and to the posterior cusp was attached a small thrombus. The aorta was considerably scarred by syphilitic lesions, with practically complete occlusion of the orifice of the right coronary vessel. The remainder of the artery was normal, and the left coronary artery was normal throughout.

CASE 7.—A 49-year-old negro man gave a story of chills, fever, and shortness of breath for 2 months prior to his admission to the hospital. There had been some swelling of the feet also. Signs of cavitation were noted in the right upper lobe of the lung. The heart was normal on examination, but Roentgen ray showed some enlargement with dilatation of the aorta. Autopsy showed chronic ulcerative tuberculosis of the lungs and acute bronchopneumonia. The heart was very slightly enlarged, with considerable fibrosis and some coronary sclerosis. The aorta was dilated and scarred with typical lesions of syphilitic aortitis.

It is not to be argued that in many of the 60 asymptomatic cases, of uncomplicated syphilitic aortitis could the clinical diagnosis have been made. The degree of involvement of the aorta found at autopsy in this group showed considerable variation. Marked dilatation was found in only 3 cases, moderate dilatation in 7, slight in 10, and a normal-sized aorta was noted in 40 instances. Extensive pathologic involvement was seen in 12, moderate in 27, and only slight involvement in the remaining 21 cases. One would hardly expect symptoms to have occurred in cases in which there was only minimal involvement of the aorta. But this is precisely the stage in which specific treatment should be able to accomplish the most, and so prevent further extension of the process as to render the development of complications unlikely. And if the available methods of symptom analysis and physical examination are inadequate to allow a diagnosis to be made definitely in this stage, their usefulness is necessarily limited. In this group of cases* the diagnosis of syphilitic aortitis was not made in a single instance, and on reviewing the pathologic findings it is difficult to pick out more than a few cases in which it would seem possible to have done so. And yet this is the group in which early diagnosis is of such importance if the most is to be obtained by antisymphilitic therapy.

On the basis of this analysis, it seems reasonable to assume that uncomplicated syphilitic aortitis is an asymptomatic condition. When cardiac or respiratory symptoms occur, they have been shown in every instance to be due to some factor other than the simple aortic disease, that is to say, either to an extension or complication of the syphilitic process or to some entirely unrelated condition. If we accept this conclusion, it becomes quite clear just why so much difficulty is experienced in making the diagnosis of uncomplicated syphilitic aortitis. There are no symptoms referable to the cardio-

* The cause of death in these patients was lobar pneumonia in 11, cerebral hemorrhage in 10, abdominal aneurysm in 5, carcinoma (various) in 5, pulmonary tuberculosis in 4, various acute surgical abdominal conditions in 4, C. N. S. syphilis in 3; 2 each died of pyelonephritis, urinary extravasation, fractured skull, septicemia, pellagra, and peptic ulcer with hemorrhage; 1 died of each of the following: acute nephritis, CCl_4 poisoning, encephalitis, tuberculous meningitis, acute leukemia and acute yellow atrophy.

vascular system, the patient does not as a rule seek medical attention, and the physical signs are such that they might be easily missed on casual examination. The importance of thorough clinical and roentgenologic study cannot be overemphasized, for by these methods alone can the diagnosis be established before the condition has progressed so far as to prevent the best results being obtained by specific treatment. Accurate diagnosis depends, therefore, upon the realization that cardiac or respiratory symptoms are significant of either a complication of the original condition or of some other co-existing disease; only when every adult syphilitic patient is regarded as a possible victim of syphilitic aortitis and only when every available method is used for the detection of beginning aortic dilatation will the diagnosis of truly uncomplicated syphilitic aortitis become clinically possible.

Summary. Two hundred and eleven cases of syphilitic aortitis, proven at autopsy, have been analyzed with regard to presenting symptoms. In practically every case in which cardiac or respiratory symptoms were present, they have been shown to be due to some factor other than uncomplicated syphilitic aortitis—either to an extension or complication of the syphilitic process or to some co-existing disease. It is concluded that uncomplicated syphilitic aortitis is an asymptomatic condition, and that no criteria dependent upon symptoms are reliable in making an early diagnosis.

REFERENCES.

- (1.) Cole, H. N., and Usilton, L. J.: *Arch. Int. Med.*, 57, 893, 1936. (2.) Keefer, C. S., and Resnik, W. H.: *Ibid.*, 37, 264, 1926. (3.) Langer, E.: Cited by Moore et al. (Ref. 5). (4.) Maynard, E. P., Jr., Curran, J. A., Rosen, I. F., Williamson, C. G., and Lingg, C.: *Arch. Int. Med.*, 55, 873, 1935. (5.) Moore, J. E., Danglede, J. H., and Reisinger, J. C.: *Ibid.*, 49, 753, 1932. (6.) Warthin, A. S.: *South. Med. J.*, 24, 273, 1931.

IDIOPATHIC MYOCARDIAL DEGENERATION ASSOCIATED WITH PREGNANCY AND ESPECIALLY THE PUERPERIUM.

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THE effect of pregnancy on the heart has been a subject of considerable interest and has been discussed from many viewpoints. There is, however, one feature of cardiac disease of pregnancy

which has never received consistent attention: namely, the existence of an idiopathic myocardial lesion associated with the puerperium. That degeneration of the myocardium may be caused by pregnancy and the puerperium was surmised many years ago, but this association has never received general recognition. Among earlier writers, both Virchow¹⁰ and Porak⁶ pointed out that myocardial degeneration was not an uncommon finding in women who died in the puerperium, the former stating that the change might reach a degree comparable to that seen in classical phosphorus poisoning. More recently, Blacker² (1907) and Campbell³ (1923) have pointed out that myocardial disease unaccompanied by valvular lesions was important in producing cardiac failure during and after pregnancy. Williams¹² (1933) stated that 1.5% of cardiac deaths during and soon after pregnancy are the result of an "idiopathic myocarditis." Hermann and King⁵ (1930), in discussing the various forms of heart disease associated with pregnancy, described 4 patients who developed severe myocardial disease during the puerperium which proved fatal in 3 instances. We regard their observations as important, for during the last 4 years we have observed in 7 patients severe puerperal heart failure of a strikingly similar type. The clinical and pathologic findings in 4 of these patients are the basis of this report of what, in our opinion, is an unusual myocardial lesion.

In all of our patients, heart failure, developing insidiously in the late months of pregnancy, assumed serious and stubborn proportions during the puerperium. The clinical features were dyspnea, edema, cardiac enlargement, cyanosis, and gallop rhythm. Murmurs were not conspicuous and precordial pain was absent. Embolism was a common development, being the immediate precipitating cause of death in 3 patients and occurring probably in all of our recovered cases.

Necropsy consistently revealed gross evidence of severe myocardial disease of recent origin. Histologic study confirmed this and showed it to consist of widespread and severe focal inflammatory reaction often with necrosis and followed by fibrosis.

Another striking feature was the development of mural thrombi in the heart, secondary either to foci of subendocardial myocarditis or to myocardial dilatation and subsequent thrombus formation in the mural columnar meshwork. This was the obvious source of embolism, which was so frequent a development.

Case Reports. CASE 1.—J. C., Italian, aged 23, whose past medical history was irrelevant, suffered from dyspnea, cough, fatigue, and edema in the 8th month of her first pregnancy. These evidences of heart failure apparently disappeared after delivery on September 12, 1930, only to reappear in greater intensity upon the resumption of her usual household duties. The heart failure gradually progressed and eventually necessitated her admission to the Philadelphia General Hospital, service of Dr. David Riesman, on January 3, 1931.

Examination revealed pulmonary congestion, an enlarged liver, and peripheral edema. The heart was moderately enlarged, its rate rapid, its rhythm regular. No murmurs were detected, but a gallop rhythm was present over the apical area. The blood pressure was 105 systolic, 70 diastolic. The blood count showed 3,300,000 erythrocytes, 75% hemoglobin, 12,000 leukocytes. The blood culture and urinalysis were negative, and the blood chemical studies and serum protein determination were all within normal limits. The electrocardiogram showed low amplitude, shaded ventricular complexes in all leads, with inverted *T* waves in Leads 2 and 3.

During the first week of our observation, the patient's condition improved slightly. The temperature, never high, soon returned to normal, and the pulse rate varied between 80 and 110. The patient's weakness, however, did not appreciably lessen, and the gallop rhythm persisted. A search for focal infection, dental and gynecologic, was unsuccessful. On January 28, the patient developed a burning pain in the left upper abdomen. This soon disappeared, but a similar attack occurred the following day, after which the spleen became palpable and tender. On February 5, there developed an attack of severe, sudden, upper abdominal pain, during which the leukocyte count rose to 35,000, persistalsis became absent, the abdominal wall rigid, and distention marked. Death occurred on the following day, February 6, and was attributed to mesenteric thrombosis.

Necropsy (Dr. Gunn, 5 hours after death). The heart, weighing 500 gm., was globular in shape and enlarged in its transverse diameter. The epicardium was smooth and glistening. Both ventricles were dilated and the left ventricular wall was moderately hypertrophied. The muscle was pale, grayish-brown, soft, and mottled by congestion. Near the apex, on the septal wall, adherent in the meshwork of the columnæ carneæ, was a reddish-brown thrombus, about the size of a nickel; the underlying muscle was soft and clouded. The right ventricle presented the same muscle changes noted in the left chamber, but no thrombi were present. There were no valvular lesions aside from relative insufficiency of the mitral ring. The fossa ovalis was closed.

The aorta was of normal appearance throughout. The coronary arteries were patulous, their intimal surface entirely smooth.

All the viscera showed an acute passive congestion, in addition to which there were hemorrhagic infarctions of the spleen and kidneys and mesenteric thrombosis which, with subsequent peritonitis, was the immediate cause of death.

Histology. Sections from the septum, the midportion of the posterior wall of the left ventricle and anterior papillary muscle all exhibit the same pathologic changes. The myocardium shows in many areas a marked parenchymatous degeneration; the muscle fibers are irregularly sacculated, and wavy because of the loss of cytoplasmic content. In some fields, muscle fibers and their nuclei appear slightly thicker than normal, suggesting a previous state of hypertrophy.

Necrotic foci, both large and small, are noted in a number of fields. The lesion shows more or less cellular infiltration by lymphocytes, occasional eosinophils and neutrophils, and larger cells with irregularly oblong and cuboid nuclei (Figs. 1 and 2). These are apparently nuclei of heart muscle, some being surrounded by sarcoplasm in a decadent state; at the periphery of such a focal lesion and in the adjacent myocardium, an earlier stage of the myocardial destruction is noted in which the myocardial cytoplasm can be seen to be disappearing, leaving behind the isolated nuclei (Fig. 2). Occasionally two or three myogenic nuclei are closely clumped together, probably representing an effort at myocardial regeneration. Some of the arterioles and venules show a slight hyperplasia of the lining endothelium; aside from this, there is no vascular damage.

The endocardium in some places is swollen by edema. These swellings contain a considerable amount of fibrinous deposit and some round and endothelial cell infiltration. The overlying endothelial layer shows disruption in a few areas with deposition of small amounts of fibrin.

CASE 2.—J. M., Polish, aged 38, had had 6 pregnancies during 11 years, during each of which she went through an episode which was diagnosed as nephritis. During the 5th pregnancy, breathlessness and edema were apparently marked, and the blood pressure was found to be high. Her 6th and last pregnancy terminated on November 21, 1931, with no complications except rather severe postpartum hemorrhage. Instead of the usual puerperal recovery, breathlessness, weakness and edema appeared and became progressively worse, and ultimately led to her admission to the Philadelphia General Hospital, service of Dr. A. A. Stevens, on January 15, 1932.

Congestive heart failure was evidenced by orthopnea, cyanosis, greatly distended neck veins, pulmonary and hepatic congestion, ascites, and marked leg edema. The heart was overactive and definitely enlarged, both by percussion and Roentgen ray examination (Dr. H. Ostrum). No murmurs were heard, but a prominent gallop was demonstrable over the apical area. The cardiac rhythm was regular. The blood pressure was 162 systolic and 124 diastolic.

Pelvic examination revealed nothing abnormal. The blood count, the Wassermann test, and the urinalysis were normal. The blood sugar was 100 mg. %, and the blood urea nitrogen 11 mg. %.

During the first few days of hospitalization, there was considerable improvement, but the gallop rhythm persisted. On January 31, 1932, the temperature rather suddenly rose to 102° F., the pulse to 140, and the respirations to 33 per minute. Signs of consolidation in both lower lobes, accompanied by a right-sided friction rub, suggested the early development of pneumonia, though the possibility of infarction was considered. The temperature soon declined and on February 8 was normal; but the pulse rate remained high and the leg edema, which had never subsided, progressively increased, and the right arm began to swell.

Death occurred on February 19, 1932. The cardiac failure was well recognized, but the character of the pulmonary consolidations remained doubtful, and the final clinical diagnosis was recorded as lobar pneumonia and myocardial degeneration following pregnancy with extreme cardiac decompensation.

Necropsy (Dr. William Brody, 13 hours after death). The significant changes involved mainly the cardiovascular system.

The heart was considerably enlarged, weighing 480 gm. The left ventricle was both hypertrophied and dilated, its wall in its midportion measuring 18 mm. The muscle was very soft and pale. The right ventricle, similarly dilated but not hypertrophied, showed the same pallor and softness. At the apex of this chamber were soft, white, loosely attached antemortem thrombi. No definite auricular thrombus formation was noted. The foramen ovale was completely closed. The coronary vessels were smooth and patulous throughout, and the aorta showed nothing of importance.

There was marked passive congestion of the viscera, in addition to which there were bilateral hydrothorax, large multiple hemorrhagic infarctions of both lungs, infarction of the liver, acute multiple ulcerations in the lower ileum and ileocecal junction, which on microscopic examination proved to be due to thrombotic occlusions of sclerotic mesenteric arterial branches.

A small, old, and firmly attached aseptic thrombus was found in one of the ovarian veins, apparently of the type seen so often after pregnancy in the tortuous veins of the broad ligaments. We regarded it as inactive and not in any way the cause of the cardiac decompensation, the massive pulmonary infarctions, or the systemic embolism.

The kidneys showed a mild nephrosclerosis and passive congestion.

Histology. The epicardium is normal. Sections from both the left and right ventricle show marked parenchymatous degeneration associated with considerable interstitial edema. In many areas, the myocardial fibers have become thin and of irregular width due to the diminution of the sarcoplasmic content; often the muscle destruction is intense so that small fragments and fibrils remain in a space devoid of any normal structure; edema and sometimes hemorrhage fill in these spaces. An occasional neutrophil is seen, but the cellular invasion is scanty; occasionally a myocardial nucleus is seen with most of the cytoplasm destroyed. In other areas, fibroblasts are invading the foci of muscular degeneration.

Some small arterial branches have definitely thickened walls, but are patulous and appear to have no relationship to the destructive change.

Kidneys. A moderate nephrosis is seen in the proximal convolutions and tubular structure. The glomeruli are congested; but there is no exudative or proliferative process suggestive of glomerulonephritis either acute or chronic. There is moderate but definite thickening of the arterioles, but no renal, parenchymal scarring is seen.

CASE 3.—S. F., aged 37, the mother of 4 healthy children, began to have breathlessness, cough, and slight edema in December, 1931, in her 3d month of pregnancy. Following a 7th month miscarriage in April, 1932, the circulatory weakness increased significantly with the appearance of marked dyspnea, edema, and hemoptysis. Bed rest and medical treatment were of no avail and she was admitted to the Philadelphia General Hospital on the service of Dr. A. A. Stevens, in August, 1932. The past medical history was otherwise unimportant. Her previous pregnancies had been uneventful and there was no history of rheumatic or other infection.

On admission, the patient showed extreme congestive heart failure, which necessitated thoracentesis, paracentesis abdominalis, venesection, and the use of oxygen. These emergency measures resulted in considerable improvement. Examination on the next day showed cardiac enlargement, which was confirmed by Roentgen ray examination. There were no murmurs, but the heart sounds were rapid and embryocardial. The blood pressure was 150 systolic and 90 diastolic. An electrocardiogram revealed the presence of numerous ventricular extrasystoles, arising apparently from different foci, low amplitude of the *Q-R-S* complexes in all leads, and inverted *T* waves in Lead 1. Clinical and Roentgen ray examination of the lungs revealed at no time any change except bilateral hydrothorax.

In spite of treatment, including the use of Novasurol, some degree of anasarca was constantly present. No focal infection was found except that associated with a bed sore over the buttocks that had developed during the many months of bed confinement and which was almost certainly the source of the *Staph. aureus* bacteremia that appeared a few days before death on September 17, 1932. The Wassermann reaction, the blood-sugar determination, and the urinalyses were normal. The blood urea nitrogen ranged between 9 and 16 mg. %; blood creatinine was 1.8 mg. %. The blood count revealed 3,750,000 erythrocytes and 17,400 leukocytes with a 90% neutrophil count. The clinical diagnosis was chronic myocarditis, possibly of the Fiedler type, with severe circulatory failure, decubitus, and septicemia.

Necropsy (Dr. Kennedy, 12 hours after death). The heart weighed 510 gm., was considerably enlarged, of globular shape, and exceedingly soft. The dilatation far overshadowed whatever previous hypertrophy had existed. On repeated section, the myocardium showed a marked parenchymatous degeneration, being pale, brownish-gray, and in the papillary muscles, a dirty putty color. Fine scarring was noted throughout. The right ventricle was likewise soft and pale, but to a lesser degree. At its apex, however, there was a grayish-white, endocardial (mural) thrombus,

organized and continuous with a fibrotic reaction in the underlying myocardium. Both auricles were dilated, and there was a dry fleshy-red thrombus attached in the right appendage.

A small, soft, greenish flagellated thrombus (*Staph. aureus*) was rather firmly attached to the edge of the anterior mitral leaflet, which was otherwise entirely normal, showing no previous lesions.

The root of the aorta and the coronary vessels were normal. Also noted were: 1, Marked cyanotic induration of the viscera; 2, large purulent bed sores over the buttocks, and, 3, a small (30 cc.) indurated right retro-mammary collection of pus and milk, the possible significance of which will be discussed later.

Histology. A number of sections taken from the wall of the left ventricle anteriorly and laterally, and from the septum show the same pathologic change: a focal destruction of muscle. Some degree of hypertrophy is occasionally noted. Many of the foci are old lesions, being really acellular scars, irregular in outline, and sometimes coalescent (Fig. 4). Subacute lesions are noted in which there is cellular infiltration including large phagocytes, loaded with blood pigment. Some destruction of the myocardium goes on at the periphery of these lesions, the sarcoplasm being involved to a greater degree than the nuclei. The latter are often surrounded by small remnants of poorly striated cytoplasm or are found isolated altogether in the focal necrosis. In all sections, the large arteries are entirely normal. In some of the old scarred lesions, arterioles are found with greatly thickened walls. This, however, is not uniform and in the subacute lesion this arteriolar thickening is not present. There is no vascular occlusion, and no septic infarctions are seen. The scars have no definite relationship to the location of the vessels.

A section of the right ventricle shows an organized mural thrombus adherent to the endocardium and merging with a subchronic fibrous lesion of the myocardium, such as is described above.

Sections from the kidney show that the large majority of the glomeruli are normal. There are occasional foci of lymphocytic infiltration with scarring of the adjacent glomeruli due to arteriolar sclerosis. The small arteries and arterioles have moderately thickened walls. There are also a few small foci of suppuration apparently early abscess formations related to the bacteremia.

CASE 4.—W. P., a white woman, aged 38, had mild dyspnea in the last 3 months of pregnancy, at which time a systolic mitral murmur had been noted. These were not striking, and did not interfere with the completion of pregnancy and a normal delivery on March 15, 1933. On attempting to resume her normal activities, however, 18 days after delivery, circulatory failure definitely developed and finally necessitated admission to the Philadelphia General Hospital, service of Dr. W. E. Robertson, on April 20, 1933.

Examination presented a definite but moderate degree of congestive heart failure, there being distention of the neck veins, râles at the base of the lungs, moderate breathlessness, and edema. The heart was greatly enlarged, the apical beat palpable in the fifth interspace in the anterior axillary line. The heart sounds were poorly heard at the apex, but the second pulmonic sound was greatly accentuated, and there was a systolic and presystolic apical murmur; auricular fibrillation was present. The blood-pressure reading was 110 systolic and 60 diastolic. The temperature varied from 98° to 100°, but after a few days returned to normal. The urinalysis, the Kahn test, and the blood sugar determination gave negative results. The blood urea nitrogen was 16 mg. %, and the blood count showed 3,000,000 erythrocytes, 60% hemoglobin, 10,900 leukocytes, with a differential of 76% neutrophils, and 24% lymphocytes.

The restoration of compensation was interrupted by cerebral embolism on May 24, resulting in a right-sided hemiplegia. Death occurred 6 days later. The clinical diagnosis was rheumatic heart disease, mitral stenosis, auricular fibrillation, and cerebral embolism.

Summary. A patient, aged 38, non-hypertensive, with known chronic rheumatic mitral valvulitis, developed severe congestive heart failure comparatively late in the puerperium; a slow recovery was ended by fatal cerebral embolism.

Necropsy (Dr. David Fishback, 14 hours after death). In addition to mitral stenosis, there was an unusual myocardial degeneration; namely, widespread necrosis with the formation of numerous mural thrombi in the left and right ventricles. There were multiple infarcts in the lungs, in the spleen, and thrombosis of the right cerebral artery with subsequent softening in the right motor area and internal capsule. There was widespread passive congestion, but no evidence of nephritis.

The heart was enlarged and of globular shape; the epicardial surface was entirely smooth. Section showed no hypertrophy, but the dilatation was unusual in that advanced fibro-calcareous mitral stenosis was present. The myocardium showed numerous foci of hemorrhagic necrosis throughout the lateral, the posterior, and to a lesser extent, the anterior walls. They extended into the apex. Both confluent and isolated areas of hemorrhage and softening were surrounded by less soft but putty-colored myocardium. The overlying endocardial surface was speckled with mural thrombi.

The right ventricle was moderately dilated, and its wall likewise contained isolated foci of hemorrhagic necrosis.

Both auricles were markedly dilated. No pectinate thrombi were seen. The fossa ovalis was open along its anterior edge so that a pencil could easily be passed; the fossa bulged out toward the left auricle and the free edge had a roughened appearance, being studded by fibrin; a tearing of the fossa with resultant patency was indicated. The coronary arteries, as far as gross inspection would permit, were of normal appearance.

Histology. A section of the left ventricle shows a myocardial lesion that is found in every section taken from either left or right ventricle, the septum included.

The epicardium is normal. In the myocardium are large and small foci of muscle destruction more intense and diffuse in the inner half of the myocardium but observed even in close proximity to the epicardium. Some of these areas are so large as completely to take up low-power fields. The muscle is replaced by densely cellular collections, in many places accompanied by hemorrhage. The cells, most of which are oval, usually have a striking tendency to lie in the same direction with each other and with the surrounding myocardial fibers so that one gets the impression of numerous rows almost parallel and continuous with the adjacent myocardial fibers (Fig. 5). Higher magnification shows that these rows of cells are really myogenic nuclei, left stranded by an apparently rapid loss of the sarcoplasm (Figs. 6 and 7). The compact disposition of these rows of nuclei give the impression of a state of tissue collapse. There are also present remnants of the interstitial connective tissue of the myocardium (perimysium). Comparatively few polymorphonuclears are seen; in large lesions, flooded by hemorrhage, neutrophils are present in modest numbers. In the smaller foci, a few lymphocytes are present, and young fibroblasts are seen in most of the lesions. At and near the periphery of the lesion, adjacent muscle fibers have become narrow and taper into wavy remnants which stain poorly. In this process of degeneration, the nuclei are also involved, but to a lesser degree. They are often swollen, somewhat to giant-cell dimension, in contrast to the progressive loss of the sarcoplasm and fibrils. Where there

has been hemorrhage, a number of macrophages are found filled with blood pigment.

In some areas the cellular collections have apparently disappeared, leaving an almost acellular structure consisting of a rather condensed fibrillar network of a few connective-tissue nuclei and many congested small vessels. This is apparently a subchronic stage: a collagen fibrosis secondary to the subacute stage of collapse. Where the myocardium is still preserved but obviously undergoing degeneration, the acidophilic stain gradually diminishes, fading out altogether or occasionally becoming mildly basophilic.

These focal lesions reach the endocardium, which in places is thickened by fibrosis and in other places covered by large fresh mural thrombi.

The large arteries and veins are patulous and without evidence of atheromatous degeneration (Fig. 8). In the midst of the areas of myocardial destruction, many small arteries are found to be filled with fresh blood, but not thrombosed. An occasional small vein is acutely thrombosed, but where these small vascular occlusions have developed they are recognized as very recent events, entirely out of relationship to the vast amount of destruction and the subacute character of the lesions.

In no place, despite the presence of mitral stenosis, is there a histologic change that can be ascribed to rheumatic fever.

We have observed the development of puerperal heart failure in 3 other patients, who after a stormy and prolonged puerperal convalescence, recovered with apparently complete restoration of compensation. We believe that their cardiac failure which was complicated by embolism, was identical with the condition just described. These cases, unsupported by pathologic data, have not been included, but occasional reference to them will be made in discussion of some of the clinical features of this cardiopathy.

Discussion.—We do not wish to imply that we believe the form of severe myocardial degeneration described in these cases of puerperal heart failure is specifically dependent upon pregnancy and the puerperal state. Instead, there is some evidence against such a view. We have encountered it at least twice in men.* Nevertheless, the observations of Hermann and King, and our own, make us feel that severe and often fatal myocardial degeneration which can only be called idiopathic can be directly or indirectly associated with or precipitated by pregnancy and the puerperium, and deserves emphasis.

The Course and Clinical Manifestations. These patients had symptoms suggestive of cardiac embarrassment before confinement, usually of a mild type and scarcely distinguishable from the general discomfort experienced by many women in the late months of pregnancy. In Case 3, however, the onset was early with leg edema and dyspnea appearing in the 4th month. Labor was hastened in one of the surviving patients because of rapidly developing toxemia; otherwise, the delivery in every instance (inclusive of surviving patients) was practically uneventful and certainly without those

* One such example, a man, aged 37 years, who developed heart failure following an upper respiratory infection, was recently reported by Roesler and Soloff.⁷

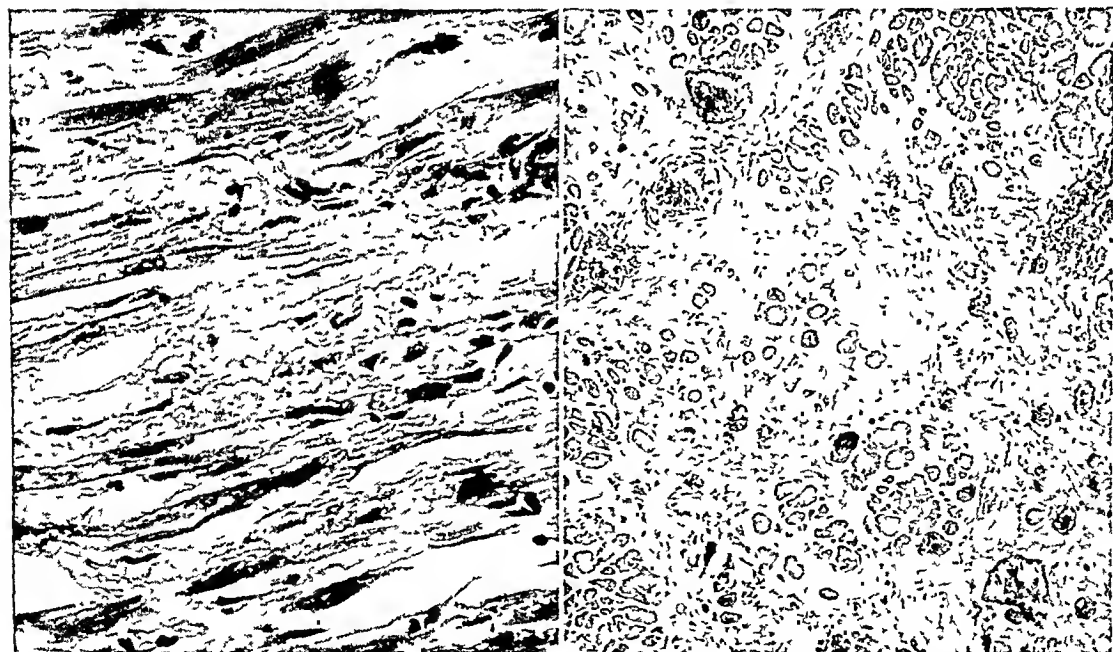
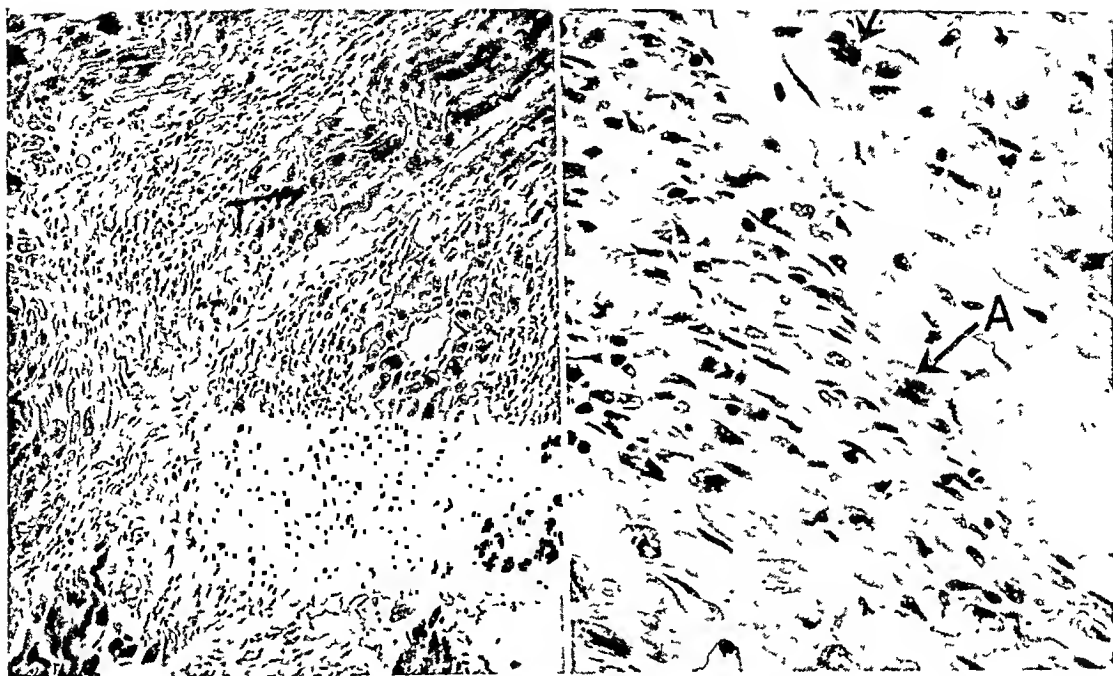
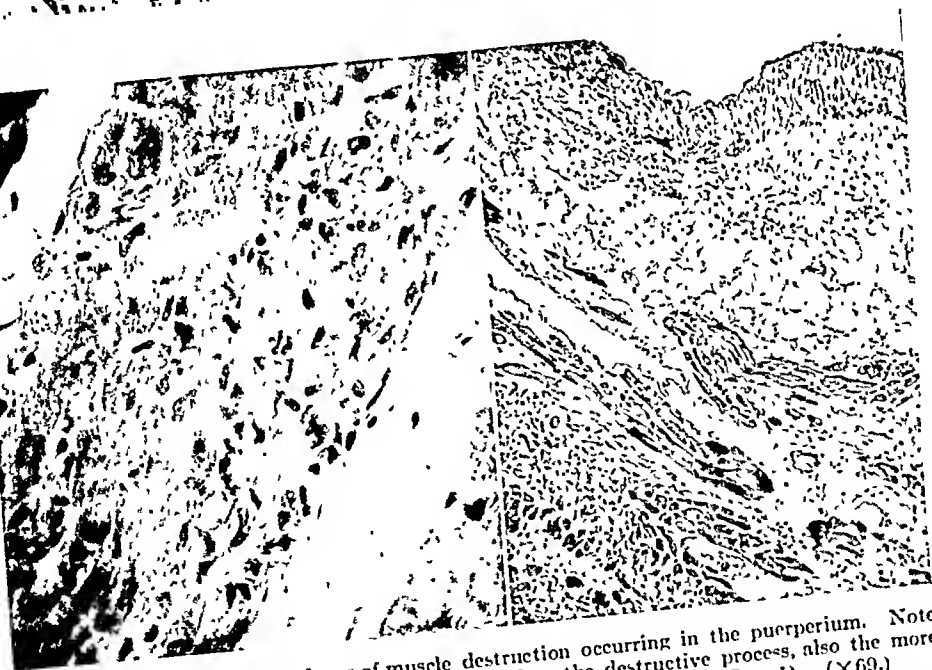


FIG. 1.—A focus of myocardial degeneration (left ventricular septum). Notice "cells" arranged in formation more or less parallel with adjacent muscle fibers. Most of these "cells" are muscle nuclei; their large size is striking even with this magnification. ($\times 92$.)

FIG. 2.—(Case 1.) Left ventricle, anterior lateral wall. Note destruction of myocardial fibers with the liberation of swollen degenerated nuclei. "A." There is a moderate number of round cells in the field, an occasional eosinophil, and also remnants of the original connective tissue. Many muscle nuclei lost in this focus and becoming progressively less characteristic, can be confused with fibroblasts. ($\times 230$.)

FIG. 3.—(Case 1.) Muscle degeneration progressing to a state of almost complete dissolution, leaving a mesh of crumpled fibrils. The degenerated nuclei are surviving the sarcoplasmic destruction. ($\times 276$.)

FIG. 4.—(Case 3.) Irregular scars, the end stage of the destructive process, in a patient who was in a state of puerperal and postpuerperal cardiac decompensation for 5 months. There are no vascular lesions. The small arteries and veins are normal. ($\times 69$.)



- FIG. 5.—(Case 4.) Large focus of muscle destruction occurring in the puerperium. Note tendency of the adjoining myocardium to "melt" into the destructive process, also the more or less parallel disposition of the muscle nuclei. Compare with Fig. 1 (Case 1). ($\times 69$.)
- FIG. 6.—(Case 4.) Almost complete sarcolysis; a few remnants of myocardial cytoplasm remain in a "cellular focus," consisting of surviving but degenerated myogenic nuclei, perimysial tissue and a few lymphocytes. This section is unfortunately marred by a granular fixation defect. ($\times 230$.)
- FIG. 7.—(Case 4.) A small focus of myocardial dissolution, "sarcolysis," entirely similar to the larger foci. ($\times 230$.)
- FIG. 8.—(Case 4.) The myocardial degeneration is seen approaching the epicardium. The coronary artery is normal. ($\times 57$.)

circulatory crises—cardiac collapse, pulmonary edema—that are not uncommon in patients with mitral stenosis. Cardiac failure in all these patients developed its most serious phases during the puerperal state. In some, the puerperal rest period appeared to pass uneventfully, only to be followed by recurring heart failure after resumption of the ordinary household activities. In Case 3, and also in one of the recovered cases, heart failure was ushered in sharply soon after delivery by hemoptysis, apparently due to pulmonary infarction. Regardless of the initial development, cardiac failure was established in each case in less than 1 month following confinement.

While circulatory weakness was fairly obvious, the symptoms and signs of heart failure were complicated as in Case 1 by other symptoms suggestive of obscure inflammatory processes. Thus, in one or another case, phlebitis, pelvic infection, and subacute bacterial endocarditis were suspected.

The fever shown by these patients was usually mild, irregular, and soon subsided to a normal level, but often there was an abrupt change in the clinical course because of embolism and infarction.

Leukocyte counts varied from 10,000 to 17,000; higher counts were obtained with the development of embolism. The differential counts were not noteworthy, except in Case 3, where a high neutrophilic response was probably due to the presence of terminal bacteremia. These patients had a secondary anemia, usually moderate. However, in Case 1, the erythrocyte count was 3,000,000 and a tentative diagnosis of the so-called pernicious anemia of pregnancy was considered.

Blood cultures were done on 3 of the 4 necropsied patients. One was positive, that being a *Staph. aureus* culture that was obtained in Case 3 after the patient had been ill for several months, and which we considered to be due to a terminal bacteremia caused by an extensive bed sore.

Decompensation was unduly prolonged in our judgment in comparison with other types of heart disease with the exception of severe chronic coronary disease. Breathlessness was common to all cases, as might be expected; it was persistent and the last symptom to disappear. Edema also afforded a striking evidence of decompensation; it subsided in Case 3 before death occurred from septicemia.

Gallop rhythm, an early and conspicuous sign, was noted in 5 of 7 patients, and its early development was matched by its persistence.

The electrocardiographic studies indicated that myocardial damage had occurred in every patient, but gave no definite clue as to etiology. Inversion of the *T* waves was seen in the various leads, either singly or in combination, allowing an interpretation of "myocardial degeneration," but never positive for myocardial

infarction. The new direct chest leads were used in one of the surviving cases.

Roentgen examination invariably showed a moderate enlargement of the heart in the transverse diameter, usually associated with pulmonary congestion. No other features were noted that would throw light on this particular type of cardiac failure.

Embolism. Embolism, usually involving the lungs and the brain, was a common occurrence, being the cause of death in 3 patients. It was thought to have been present clinically in 3 recovered cases. This complication had its origin not in thrombotic valvular disease, but in mural endocardial thrombi. This was certain in Cases 1 and 2 and most probably so in Case 4, despite the presence in the latter of mitral stenosis and auricular fibrillation. Embolism was present not only in the terminal phase, but was also one of the early developments of cardiac failure as indicated by the occurrence of hemoptysis a few days after delivery in Case 3. Hermann and King⁵ noted passive pulmonary infarction, the origin of which they attributed to chronic passive congestion of the lungs and "acute parturient slowing of the movement of the blood mass," secondary to a myocardial degeneration. Our pathologic observations, both gross and histologic, led us likewise to believe that the pulmonary infarctions have their genesis in a weakened and diseased myocardium, but, contrary to the thought of Hermann and King, we feel that the origin of these infarctions is related to embolism: that mural thrombi, as demonstrated in our necropsied cases, are formed within the heart as a result of severe muscle degeneration, which in some cases is comparable in its severity to that seen after acute coronary occlusion, or else they are formed as a result of static thrombus formation in the mural meshwork of dilated auricles and ventricles. This view of the origin of the pulmonary infarctions receives support from the occurrence of the cerebral and other systemic embolisms that were noted so frequently in the same patients.

Histopathology. The histologic changes are unlike those seen in the common forms of myocardial failure. The lesion is focal, but in Case 4 had become remarkably conglomerate and diffuse throughout both ventricles. Two of the hearts showed what may be termed the acute stage of the lesion; a third case showed numerous old lesions and some in the subacute stage; a fourth showed gradation from the chronic to a fairly active subacute stage. The older fibrotic lesions were perhaps best seen in Case 3, where they occasionally occurred in a perivascular location, but more often were scattered indifferently throughout both ventricles independent of vascular relationship. For this reason, we believe that the chronic changes represent a healed focal myocardial lesion of an idiopathic type.

The outstanding feature noted in the acute and subacute phases

appears to be a disintegration of the myocardial fibers involving the nuclei to a lesser extent so that the latter remain as a conspicuous and often major element in the cellular collection that has replaced the myocardium. Hemorrhage into these areas is a rather common finding. A moderate number of lymphocytes and macrophages, occasional neutrophils and also eosinophils (Case 1) are present, but the myocardial nuclei are found in practically every active lesion, indicative of a sarcoplasmic degeneration rather than an interstitial infectious inflammation. They are seen at the periphery of the focus, stranded by the dissolution of their cytoplasm or already adrift, mingling with the cells of the fixed tissue. In some fields these nuclei remain standing in more or less parallel rows, approximately their normal position, but now somewhat more compact, as if they have been compressed by the pressure of the surrounding myocardium. As these lesions become older, they are invaded by fibroblasts, the original myocardial nuclei disappear, and ultimately acellular scars replace the lesion.

Occasionally, two or more nuclei are clumped together in small "giant cell" formation at the periphery of the lesion. They probably represent some attempt at regeneration. The pathologic change is not confined to focal destruction. In many fields the muscle structure is intact, but the fibers show marked degenerative changes, the sarcoplasm apparently being reduced in amount so that the fibers twist or become sacculated, their striations lost, and occasionally they end up in a mass of tangled fibrils. The focal necrosis may represent only an advanced stage, which was originally preceded by a mild diffuse non-necrotic involvement of the muscle. If this be true, it would appear reasonable to believe (this, of course, is hypothetical) that less severe forms of this myocardial degeneration occur not infrequently and eventuate in recovery; whereas, the pathologist will encounter only occasional instances of what apparently, at least from his viewpoint, is an uncommon form of cardiac failure.

The arteries were found to be patulous throughout. The arterioles showed moderate thickening in the scarred areas, but not in the early destructive lesions. The histopathologic changes of neither rheumatic carditis nor lues were present in any case, nor the type that we associate ordinarily with hypertensive heart disease.

The Relationship of Possible Nephritis and Hypertension to Puerperal Heart Failure. The blood-pressure readings in patients (Cases 2 and 3) indicated a mild hypertensive state. The systolic blood pressures ranged between 150 and 160; the diastolic pressures between 90 and 120. Eyeground examination done in 2 patients showed nothing of diagnostic importance. The heart weights in the 4 necropsied cases, 2 of which were known to have had hypertension, showed a definite increase over the normal, ranging from 450 to 500 gm. It is accepted that a heart weight of 450 gm. and over in

the absence of other provocative factors is evidence of idiopathic hypertension, although blood-pressure readings may have been normal or lower by the time the patient came under observation. However, the increase in weight may well have been due to the many degenerative and necrotic lesions throughout the myocardium and to the considerable edema. It is possible, therefore, that hypertension may have been a factor in this unusual cardiac degeneration, but the number of cases studied is entirely too small to permit us to draw any conclusion. Case 1, it is to be noted, definitely did not have hypertension. We wish to emphasize that, in our opinion, hypertension was not responsible as a sole cause for the cardiac lesion. Our reasons for this conclusion are that neither the clinical nor the histologic pictures conformed to those seen in either the malignant or the chronic hypertensive state.

It is almost a matter of tradition to invoke a nephritic factor in severe edematous states in pregnancy and the puerperium. Every one of our patients was regarded as nephritic, either on admission to the hospital or by the private medical attendant. The diagnosis of nephritis has to be supported by laboratory evidence which was practically negative in all cases except for a short interval of toxemia in one of the surviving patients, and in that instance the renal-toxic symptoms quickly abated after delivery. Case 2 had been treated for nephritis since the first attack of decompensation 11 years previous to the final childbirth and eventual cardiac death. Necropsy revealed essentially normal kidneys. There was a moderate arteriolar sclerosis as evidenced by thickening of the small vessels in the spleen, kidney, and to a lesser degree in the myocardium. These findings were in accord with the history of comparatively recent and mild hypertension. In Case 3, there was a small area of necrosis in one kidney, apparently an early septic infarct incidental to the staphylococcus bacteremia. The large majority of the glomeruli and the kidney as a whole presented a normal appearance. The kidneys in Case 1 were normal except for small infarcts and congestion, and in the remaining autopsied case (Case 4), also were normal.

The Relationship to Infection. The finding of a so-called "primary myocarditis" or "myocardial degeneration" in cases of women recently delivered suggested the possibility of a causal influence by focal infection connected with gestation. Investigation from that angle was fruitless. Gynecologic examination was negative, and this was verified in the 4 necropsied cases. One of the women (Case 1) may have had phlegmasia alba dolens for a short time after delivery. However, when she came under our observation, there was no evidence of phlebitis or lymphangitis.

Any case showing obvious pyemia would necessarily be rejected on the supposition that its clinical-pathologic aspect would be ob-

scured. In Case 3, there were two conditions which must be considered before the severe myocardial change that was present could be ascribed to the idiopathic influences of pregnancy and the puerperium: 1, This patient died with a *Staph. aureus* bacteremia, which we believe was a terminal event, resulting from a stubborn bed sore that had developed after 3 months of cardiac decompensation; 2, necropsy also revealed a collection, approximately 30 cc. of inspissated milk and pus behind the right breast which gave neither signs nor symptoms, and was not recognized during life. Microscopically, it was found to be a chronic lesion, probably originating after the patient's miscarriage. We do not see how this lesion, which may conceivably have been infectious, could have been the cause of the myocardial failure; first, because latent encapsulated, clinically quiescent, breast abscesses are by no means rare, and so far as our knowledge goes, have never been associated with myocardial failure; second, heart failure in this instance began before the miscarriage, and presumably, therefore, before the development of the mammary lesion.

The clinical picture and also the gross morbid anatomy in our patients was similar in many ways to that rare form of subacute idiopathic myocarditis occasionally reported under the synonym "Fiedler's myocarditis."⁹ The etiology in that disease is thought to be infectious, but in view of the remarkable diversity of disease states that have preceded cardiac involvement, one must conclude that the term "Fiedler's myocarditis" is a little more than a convenient name for myocardial inflammations that do not fall into standard classifications. In the large majority of case reports of isolated idiopathic myocarditis, the authors have stressed the interstitial and apparently distinctly infectious character of the lesion.^{1,4} In a few cases there has been an associated parenchymatous involvement with dissolution of the myocardial substance and the appearance of "myogenous" cells,⁸ similar in some degree to the histologic picture in our own material, and it is possible that some of the cases of subacute idiopathic myocarditis were identical with those comprising this report. However, as far as we can ascertain, no reference has ever been made to pregnancy or the puerperium as having any bearing on the clinical course or possible etiologic relationship to the lesion.

The Possible Relationship to Thyrotoxicosis. We mention this because of the occasional reference to the possible influence of thyroid disturbance in the "toxic cardiorenal state" of the puerperium.¹³ There are also occasional reports of focal myocardial necrosis in the very severe states of thyrotoxicosis.¹¹ Marked sarcolysis, however, was not featured, nor was embolism noted either in Weller's case or in a patient of our own who showed focal myocardial degeneration associated with advanced toxic goiter.

We considered the possibility of thyrotoxicosis, but since none of the patients showed any sign or symptom suggestive of the disease, and since it was felt that the state of the patients precluded accurate determination, basal metabolism studies were not done on any of the necropsied cases. In 1 recovered case, the basal metabolic rate was + 12%.

Etiology. It is impossible for us to form any definite opinion as to the etiology of this lesion. The majority of these women began to have cardiac embarrassment in the late months of pregnancy. Every case, however, developed it to its most serious degree in the puerperal state, which is opposed to the usual behavior of toxic phenomena in parturient women, since such phenomena ordinarily are quickly terminated by delivery. These facts suggest to us that probably more than one factor may be responsible; that some process in the puerperium may aggravate and prolong whatever cause for cardiac embarrassment existed before confinement. It is reasonable that cardiac muscle made vulnerable by previous disease such as hypertension, rheumatism, or possibly other infection, may be more readily damaged by the unknown puerperal factor than will be the case with normal hearts. Beyond the statement of these few facts, discussion of the etiology becomes hypothetical. The pathologic-physiologic status of pregnancy is very complex, and many diverse possibilities have therefore come to mind, such as calcium deprivation, dietary deficiencies, the action of proteolytic enzymes, and the administration of ergot. Some of these speculations could be dismissed on the basis of the available clinical data, but since we have not been able to subject any of them to the control of detailed clinical research, the solution for the problem remains for future study.

Summary.—1. A clinical study was made of 7 women having cardiac decompensation in the puerperium. Four of these patients died, and at necropsy showed a myocardial degeneration differing from the lesions ordinarily associated with the current classification of heart disease.

2. The coronary arteries were normal and there was no evidence of coronary occlusion in the living patients.

3. Death occurred in 3 cases following embolism, which had its origin on the endocardial surface of degenerated heart muscle. No other proven source of embolism was found.

4. Pulmonary and cerebral embolism were notable. Slight patency of the foramen ovale, apparently due to recent pressure changes within the right auricle and allowing the passage of a pencil was present in one instance. No patency was demonstrated in the 3 remaining cases.

We are indebted to the following chiefs of service: Drs. Riesman, Robertson, Stevens and McGlynn; and to the following pathologists: Drs. Gunn, Fishback, Kennedy and Brody for the privilege of presenting these cases.

REFERENCES.

- (1.) Belientin, L.: Ztschr. f. klin. Med., 54, 290, 1904. (2.) Blacker, G. F.: British Med. J., 1, 1225, 1907. (3.) Campbell, D. G.: Canadian Med. J., 13, 244, 1923. (4.) Fiebach, R.: Virchow's Arch. f. path. Anat., 233, 57, 1921. (5.) Hermann, G. R., and King, E. L.: J. Am. Med. Assn., 95, 1472, 1930. (6.) Porak, C.: De l'influence reciproque de la grossesse et des maladies du coeur, Thesis, Paris, 1880. (7.) Roesler, R. W., and Soloff, L. A.: Ann. Int. Med., 9, 477, 1935. (8.) Saltykow, S.: Virchow's Arch. f. path. Anat., 182, 1, 1905. (9.) Scott, R. W., and Saphir, O.: Am. Heart J., 5, 129, 1929. (10.) Virchow, R.: Sitzung der Berliner geburts-huelflicher Gesellschaft, 1870 (quoted by Porak). (11.) Weller, C. V., Wanstrom, R. C., Gordon, H., and Bugher, J. C.: Am. Heart J., 8, 8, 1932. (12.) Williams, P. F.: Weekly Roster and Med. Digest., 28, 7, 1933. (13.) Wilson, R. H.: J. Am. Med. Assn., 107, 1039, 1936 (Discussion).

MYOCARDIAL ABSCESS WITH PERFORATION OF THE HEART.

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ABSCESS of the myocardium is relatively rare. In most instances it is a metastatic manifestation of overwhelming sepsis and is of more theoretical than clinical significance. The literature on the subject is meager. Most of the case reports in the older literature consist in a gross description of the heart without information on the clinical course or bacteriology. Some of these earlier cases described as abscess were undoubtedly necrosing cardiac infarctions.

In the necropsy records of the Department of Pathology of this hospital, abscess of the myocardium was noted in 31 cases, with bacteriologic data available in 26. *S. aureus* sepsis was responsible in 20 cases, pneumococcus in 2, *S. viridans* in 2, *S. pyogenes* in 1, and meningococcus in 1.

Abscess of the myocardium may rarely develop as a solitary local manifestation and lead to perforation of the heart. In the 31 cases in this hospital rupture as a result of the abscess occurred but twice. Both of these cases were observed within 1 year. The primary purpose of this communication is to report these 2 cases, and to cite similar cases found in the literature.

Case Reports. CASE 1.—J. H. (No. 803299), a 73-year-old white male laborer, was admitted complaining of shortness of breath for 4 months. For a year he had had some difficulty in urination, occasional incontinence, day and night frequency and had become very thirsty, taking 2 gallons of water daily. Although his appetite had remained good, he had lost 10

pounds. About 4 months prior to entry he began to get weak and dizzy and to have dyspnea on exertion. This increased, and finally he had also several attacks of nocturnal dyspnea in bed. He had had no chest pain and no dependent edema. His past history was irrelevant.

The examination revealed an elderly thin man lying quietly in bed in no great distress. The lips were cyanotic. The respiration was Cheyne-Stokes in character. The heart was moderately enlarged; the sounds were distant and of poor quality, and there was a faint blowing aortic diastolic murmur. There were a few moist râles at both lung bases. The abdomen, extremities and reflexes were normal. The temperature was 98.6° F., pulse 120, respirations 20. The blood pressure was 130/60 mm. Hg.

Laboratory studies revealed sugar and a trace of acetone in the urine. The blood hemoglobin was 82%; leukocytes 13,400 per c.mm. (76% neutrophils). The Kahn test of the blood was positive. The non-protein nitrogen was 33 mg., and the fasting blood sugar 95 to 124 mg. per 100 cc. Electrocardiogram revealed sinus rhythm, T_1 inverted, T_2 and T_3 upright with slightly low origin.

Course. The patient was slowly digitalized and the râles disappeared from the lung bases. Since he could not void, an indwelling catheter was inserted. His diabetes was regulated by diet and by an occasional dose of 5 units of insulin. The patient was weak, and developed decubitus ulcers, also a cystitis. On the 10th day there was a rise in temperature to 100° F. and acetone again appeared in the urine. Repeated doses of orange juice and 5 units of insulin at 4-hourly intervals cleared this state and the patient seemed better. The next day he suddenly awoke with a severe pain across the costal margins. He went into circulatory collapse, developed severe Cheyne-Stokes' breathing, and died 4 hours later.

Necropsy. The pericardial cavity was markedly distended and filled with about 300 cc. of clotted blood. The visceral pericardium was rough, granular and hemorrhagic. There was a point of rupture of the right ventricle 1.1 cm. in length, anteriorly and 3 cm. to the right of the left coronary and 1 cm. below the base of the pulmonary artery, or just below the tip of the right auricular appendage externally (Fig. 1).

The heart weighed 540 gm. There was moderate increase in pericardial fat. The right auricle and tricuspid valve were normal. The right ventricle was 0.5 cm. thick; its endocardial surface was pale grayish-brown. At a point 0.7 cm. below the base of the pulmonary valve and 2.2 cm. lateral to intraventricular septum there was a point of rupture, its inner orifice being about 0.8 cm. in diameter. Its margins were irregular and frayed with clotted blood adhesions. Over this area the myocardium was pale grayish-brown, and showed a few small, irregular, yellowish points about 0.1 cm. in diameter in a rim about 0.5 cm. wide. The left ventricle was moderately dilated and hypertrophied to 1.9 cm. in thickness. The left coronary artery was widely patent but showed numerous small yellow plaques of sclerosis in the first portion. The right coronary orifice was narrowed to 0.2 cm., but the vessel was patent.

The aorta showed marked diffuse aneurysmal dilatation of arch and thoracic portion, as well as marked diffuse patchy sclerotic thickening. The rest of the examination revealed no relevant findings.

Microscopic Examination. The ventricular wall was normal except over the pericardial surface, where a fibrinous and neutrophilic exudate was present and under which were small foci of lymphocytes. The coronary vessels were well preserved. Surrounding the ruptured area there was marked diffuse neutrophilic infiltration of pericardium and myocardium with acute necrosis of the heart muscle. The thrombus in a branch of the coronary artery contained neutrophils, lymphocytes and macrophages.

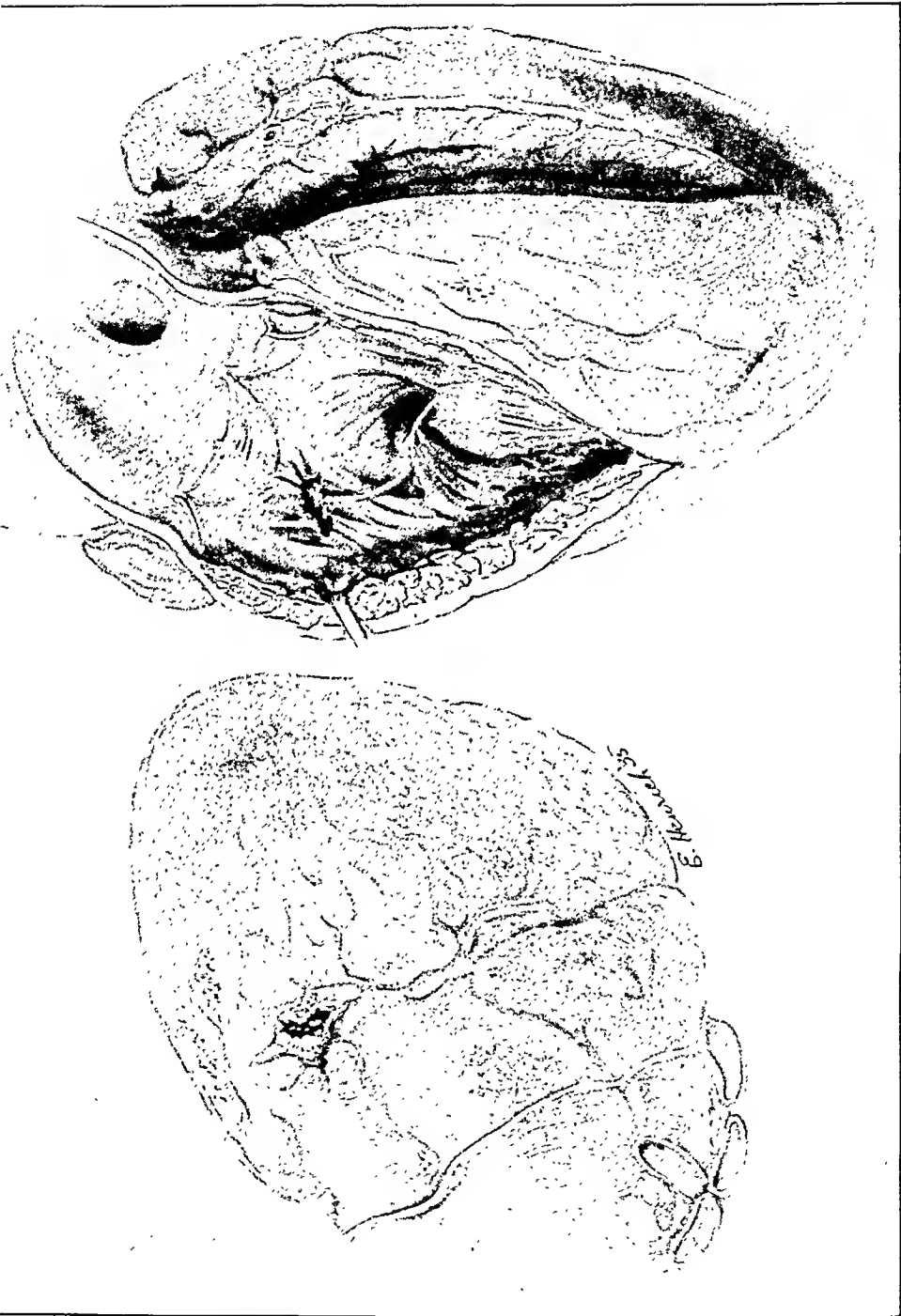


FIG. 1.—Cardiac perforation of *S. aureus* abscess. Pericardial (left) and endocardial (right) appearance of the rupture.

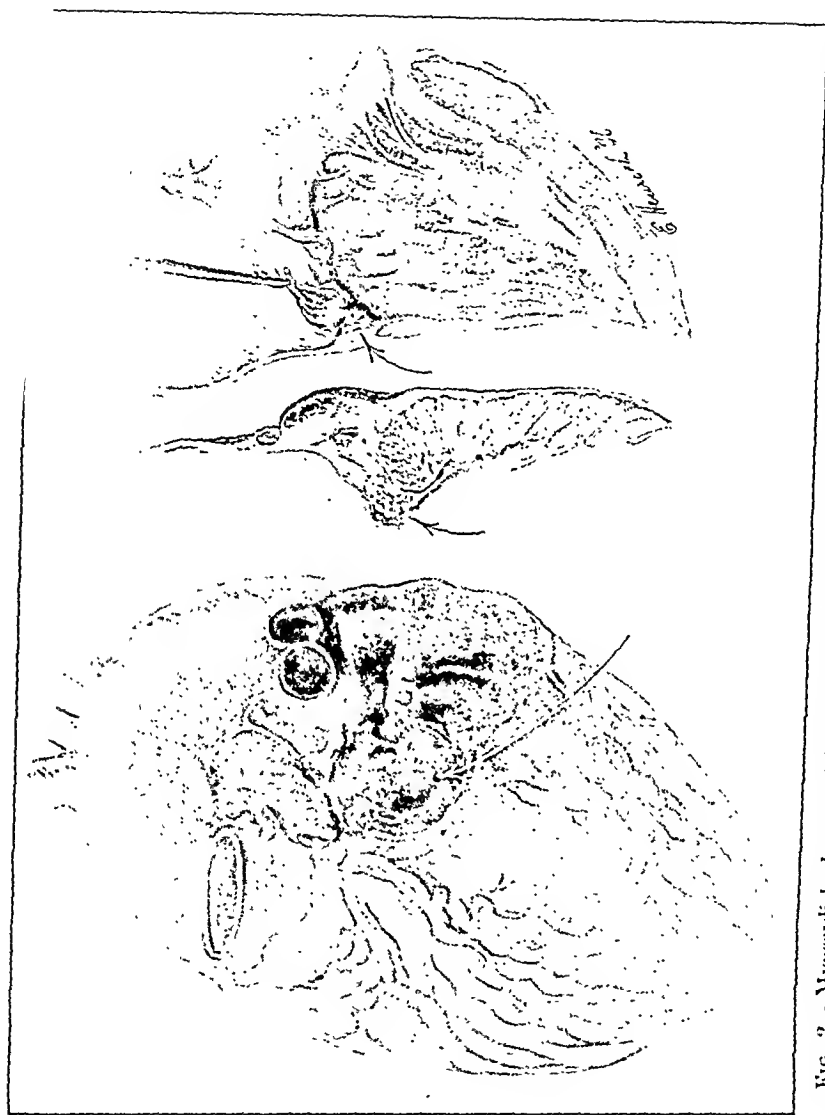


FIG. 2. - Myocardial abscess originating from an extension of a pneumococcus endocardial vegetation. Small pericardial perforation with hemorrhage (left); abscess tract between vegetation and pericardial perforation (center); and location of small vegetation under the mitral leaflet (right).

The Gram-Weigert staining showed numerous Gram-positive cocci in pairs and clusters in the abscess area. Similar cocci were noted in the thrombus and in the pericardium. Bacteriologic examination of the blood obtained from the cardiac cavity yielded a pure culture of *S. aureus*.

CASE 2.—M. McG. (No. 835250), a 78-year-old white woman entered the hospital complaining of an intermittent, throbbing precordial and epigastric pain for 2 weeks. There had been no cough, chills or fever. The past history was irrelevant.

The examination revealed an aged, poorly developed, emaciated woman lying quietly in bed and apparently not acutely ill. The heart was enlarged, with the apex impulse in the anterior axillary line. The sounds were forceful, rhythm regular, no murmurs. There were râles at both lung bases and also at the left apex posteriorly, but no dullness. The abdomen, extremities and reflexes were normal. The temperature was 99° F., pulse 110, respirations 25 per minute.

Laboratory Studies. The urine was normal except for 12 to 14 white blood cells in the sediment. The hemoglobin content was 64%, and the white blood count 25,800 per c.mm. (neutrophils 94%). The shape of the red cells and platelets was normal. The Kahn test of the blood was negative. The non-protein nitrogen was 27 mg. per 100 cc. Roentgen ray of the chest showed bronchopneumonia at both bases. An electrocardiogram showed normal sinus rhythm; the rate was 136 per minute, and there was a low origin of T in the fifth lead.

Course. There was improvement for the first 2 days in the hospital; the temperature was normal on the second day, although the pulse rose to 125 and the respirations to 35. On the 3d day the patient suddenly went into collapse, with a subnormal temperature and a drop of the pulse rate to 90. There were no new complaints associated with this episode, which terminated fatally in a few hours.

Necropsy revealed a hemopericardium, with the heart completely surrounded by about 150 cc. of blood clot and fluid. The heart weighed 260 gm. On the epicardial surface of the left auricle in the region of the mitral ring was a raised blackish-red area 3 by 4.5 cm. in size, coated with fibrin. A probe could easily be inserted into it (Fig. 2). On section it was seen to consist of necrotic epicardial fat.

In the left ventricle beneath the aortic leaflet of the mitral valve were several very small friable vegetations. In one area a probe could be easily passed upward beneath the valve into the necrotic portion of the epicardium. Microscopic section of this sinus showed blood clot, numerous neutrophils, fibrin and beginning organization. Diplococci were seen in the cytoplasm of some of the leukocytes. Culture of the abscess and also of the endocardial vegetations grew pneumococcus, Type 14. The myocardium, endocardium, papillary muscles and chordæ tendineæ were negative except near the vegetations, where there was edema and some necrosis.

The coronary arteries showed a considerable degree of atherosclerosis and a small branch of the circumflex supplying the abscess area could be traced until its lumen became almost obliterated, with no evidence of rupture.

The right pleural cavity contained 200 cc. of clear amber fluid, and the left 100 cc. The left lung was completely bound down by easily broken adhesions. The right lung weighed 480 gm. and the left 525 . The lower lobes of both lungs were dark in color, subcrepitant, and contained patchy areas of consolidation, particularly the left. On section, purulent yellow material could be expressed from scattered areas over the lower lobes. In the upper part of the left lobe there was an area of consolidation 5 cm. in diameter. The rest of the examination revealed no pertinent findings.

Discussion.—Abscess of the myocardium may rupture either into the cavities of the heart or into the pericardial sac. Howitt,⁵ in 1846, reported the postmortem findings on an 8-year-old boy who fell gradually into coma. One may assume that the cause of his ailment was sepsis. The pericardium was distended and a pint of pus was found in the sac. At the juncture of the right auricle and ventricle an abscess was incised containing a teaspoonful of pus. The abscess cavity communicated with the right auricular cavity. No statement is made as to whether the abscess opened into the pericardium. Moxon,⁸ in 1869, described the case of a boy aged 11 in Guy's Hospital, who suffered from high fever and delirium. Physical examination of the chest was not made. At postmortem examination turbid fluid was found in the left pleura. There was an acute fibrinous pericarditis. Several small abscesses were located in the myocardium. One of these had ruptured into the left ventricle. Similar abscesses were found in one kidney and in the bones. This was undoubtedly a case of sepsis of undetermined etiology. In 1884, Haddon⁴ reported 2 cases of ruptured heart. One of these occurred in a boy, aged 6, who died suddenly while suffering from a disease of septic nature. On postmortem examination, scattered abscesses of the body were found. Severe fibrinous and purulent pericarditis was present. There was a rupture of the left ventricular wall posteriorly, near its junction with the auricle and just below the coronary sinus. This opening led to a small abscess cavity which, in turn, communicated again with the ventricular cavity just below the posterior flap of the mitral valve. Endocarditis was not present. No bacteriologic examination was made. Formad,³ in 1893, demonstrated a specimen of the heart of a man who died suddenly while diving. In the left ventricular wall posteriorly an abscess, the size of a large bean, was found. The pericardium contained seropurulent fluid. Several ecchymoses were present over the pericardial surface. No mention is made of the rest of the postmortem examination, or of the etiology of the abscess. Rudolf and Moorhouse,¹⁰ in 1916, described the case of a 20-year-old soldier with normal circulatory signs who, while in the hospital with a shrapnel wound, developed a septic state. Subsequently a short systolic "swish" and a marked, rough diastolic bruit could be heard over the second and third costal spaces on the right, close to the sternum. A diastolic thrill was palpated over the same area. Necropsy revealed a pericardial sac containing yellowish fluid with fibrin and a partially resolved blood clot. On the inner wall of the dilated right ventricle, an ulcerated area opened into a narrow channel of an abscess. The latter invaded the interventricular septum, opening again just under the semilunar valve of the aorta. The pericardial wall was intact and the myocardial abscess must have been metastatic. Bacteriologic examination was not made. Stevenson and Marshall,¹¹ in 1928, described the case of a

boy, aged 9 years, who suffered from a *S. aureus* sepsis and died rather suddenly. Postmortem examination revealed a fibrinous pericarditis. The heart contained three small abscesses. Two of these ruptured into the pericardial cavity and were covered with blood clots. McLagan,⁷ in 1928, reported a case of a 57-year-old man who, following a large carbuncle, developed a generalized sepsis. In this illness he developed a "seizure" and collapsed. Postmortem examination revealed the pericardial sac filled with a soft clot. A small probe could be passed into the right coronary artery and into a small cavity containing 1 cm. of pus. Bacteriologic examination was not made.

We were able to find in the literature only these 7 cases of rupture of the heart by abscess described in sufficient detail to rule out other conditions. In 611 cases of spontaneous cardiac rupture collected and analyzed by Krumbhaar and Crowell,⁶ abscess was mentioned in only 3 instances. In 92 additional cases of ruptured hearts analyzed by Davenport,² 2 were the result of abscess. It is probable, however, that the condition is more frequent than indicated by these reports in the literature.

Abscess of the heart occurs not only in man, but also in animals. Oehl⁹ mentions that during the period of 1892 to 1921 he never observed cardiac abscess in cattle, either during meat inspection or in numerous autopsies. During the year 1921 he encountered the condition in 2 instances. The first case was that of a 4-year-old fat cow which, on the day she was butchered, had been driven a distance of 8 kilometers without difficulty. About a hand's breadth above the apex of the heart a bulging and fluctuating area about the size of a plum was found. This "silent" abscess containing creamy pus apparently did not rupture. In the other instance, the cow appeared to be previously in good health and died suddenly during the night. The autopsy revealed an abscess about the size of an egg in the lateral wall of the left ventricle. The musculature in the inside of the heart was of paper thinness and had a perforation about the size of a 10 "pfennig" piece. Dark, loose coagulated blood surrounded this area of perforation into the ventricle. The author believed that these solitary abscesses developed as a result of a cardiac lesion caused by epidemic foot-and-mouth disease, secondarily infected with the *Bacillus pyogenes*.

The 2 human cases here reported are quite unique in that no other abscesses were found in the body. In the first case, the staphylococcus abscess of the heart probably originated from urinary sepsis; in the second case, the myocardial abscess was a direct extension of a small mural pneumococcus vegetation, a complication of a bronchopneumonia. In the latter case, the abscess was localized in the fat tissue at the junction of the auricle and ventricle. As indicated from other case reports in the literature, abscesses have a certain predilection for this area.

In both of the cases reported by us the small coronary arteries traversing the abscessed area were thrombosed, but the histologic picture of the thrombus indicated that it was a secondary, rather than a primary, process. Abscess of the myocardium may, however, develop as a secondary process in a previously infarcted area caused by a primary coronary thrombosis, as indicated by the remarkable case reported by Cossio and Bereonsky.¹ A 64-year-old man suffered for 2 years from manifestations of coronary sclerosis and later thrombosis. Three days before coming to the hospital he developed thoracic pain and respiratory difficulty. During his 2 weeks' stay in the hospital he had fever, signs of bronchopneumonia and leukocytosis, and electrocardiographic changes. Gradually circulatory collapse supervened and he died. Post-mortem examination revealed a pneumococcus meningitis and myocardial abscess containing pneumococci. The latter was localized within the old infarcts. One has to assume that the infarcted area was predisposed to the formation of abscess. In support of this assumption, we have observed the formation of pneumococcus abscesses at the site of intramuscular injection of caffeine to patients with lobar pneumonia.

The clinical manifestations of myocardial abscess with rupture, as judged from the 7 cases in the literature and the 2 cases here reported, are variable. The abscess itself is usually symptomless until its rupture causes sudden precordial non-radiating pain followed by progressive circulatory collapse (pericardial tamponade) causing death within a few hours. The case of Rudolf and Moorhouse¹⁰ indicates, however, that the dissection of the myocardium by an abscessed tract can be responsible for systolic "swish" and rough diastolic bruit. The diastolic murmur heard in Case 1 may also have been caused by the opening of the abscess into the ventricle. The electrocardiogram, as indicated by the 2 cases here reported, may be essentially normal before the rupture of the abscess. It is of interest that none of the reported cases of cardiac rupture due to abscess has been diagnosed clinically.

Summary. 1. Two cases of solitary myocardial abscess with perforation of the heart are described. In the first case the abscess, caused by *S. aureus*, ruptured into the right ventricle as well as into the pericardial sac. In the second case the abscess, caused by pneumococcus, was localized mainly in the fat tissue at the junction of the auricle and ventricle and was formed as a direct extension of a small mural pneumococcus vegetation. This abscess ruptured into the pericardial sac. In both cases the clinical course did not suggest sepsis and the unexpected cardiac perforation resulted in a fatal circulatory collapse.

2. While abscess of the myocardium in cases of sepsis is not an unusual occurrence, perforation of the heart by abscess is rare. Seven such instances, collected from the literature, are cited. As

judged from the 9 cases now available, myocardial abscesses are silent until their rupture causes sudden low thoracic pain, followed by circulatory collapse. In 2 of the 9 cases a diastolic murmur was present.

We wish to thank Dr. Joseph E. Hallisey for granting permission to include the clinical abstract of Case 2.

REFERENCES.

- (1.) Cossio, P., and Berconsky, I.: *Semana méd.*, 2, 1691, 1933. (2.) Davenport, A. B.: *AM. J. MED. SCI.*, 176, 62, 1928. (3.) Formad, H. F.: *Trans. Path. Soc.*, Philadelphia, 16, 80, 1893. (4.) Haddon, W. B.: *Trans. Path. Soc.*, London, 35, 121, 1884. (5.) Howitt, T.: *Lancet*, 1, 684, 1846. (6.) Krumbhaar, E. B., and Crowell, C.: *AM. J. MED. SCI.*, 170, 828, 1925. (7.) McLagan, F.: *Lancet*, 2, 279, 1928. (8.) Moxon: *Trans. Path. Soc.*, London, 20, 113, 1869. (9.) Oehl: *Deutsch. tierärztl. Wehnschr.*, 37, 87, 1929. (10.) Rudolf, R. D., and Moorhouse, V. H. K.: *Lancet*, 1, 292, 1916. (11.) Stevenson, G. H., and Marshall, A. J.: *Glasgow Med. J.*, 110, 337, 1928.

THE RÔLE OF DISTENTION IN THE GENESIS OF ACUTE INFLAMMATION OF HOLLOW VISCERA.

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THE thesis that acute inflammatory changes may develop as a result of mechanical distention of a hollow viscus will be elaborated on in this paper. It is our impression that bacteria play a subordinate rôle in these changes and are of importance mainly in the stimulation of fluid extravasation which augments the distention factor. It is realized that this concept is in conflict with the current teachings of pathologists, but it is hoped that sufficient evidence can be adduced to lend some credence to the view.

Many of the hollow viscera of the body contain a more or less rich bacterial flora^{14,15} and this fact is responsible for the teleologic reasoning which assumes that if bacteria are found in pathologic tissues they must have an etiologic relationship. If the organ, ordinarily sterile, is found to contain bacteria and to show pathologic changes, such reasoning is acceptable. In the case of the appendix, for example, which is a tube containing many types of organisms, Wangensteen and Bowers²⁴ have shown that relatively few cases of acute inflammation show organisms in the tissues but that incidence of organisms is increased if gangrene has supervened. In this case, since the bacteria tend to appear late or not at all in the course of the disease, they cannot be assumed logically to play the important etiologic rôle. That the absorption of bacterial products is not always a factor in the production of acute inflammatory changes in an obstructed hollow viscus will be shown later.

Van Zwalenburg,^{23a,b,c,d} in his excellent papers, describes the sequence of events which leads to acute inflammation in a distended

hollow viscus, in which the lumen is obstructed. The arteries at systolic pressure carry fluid into the viscus, which is drained at a much lower pressure by the veins and lymphatics. There is fluid in the lumen, having a greater osmotic pressure than the tissue fluids. Consequently there is a shift of fluid from the vessels and tissues into the lumen, thus initiating the distention factor. Small venules become occluded and serum begins to be extravasated. As distention progresses, veins and lymphatics become further blocked by pressure within the lumen and as the blood flow is decreased, diapedesis of leukocytes begins. On the aspect of the organ opposite to that into which the vessels enter, blood supply is poorest and here the flow is first entirely blocked. The arteries continue to pump in blood and now the small venules and capillaries rupture. The tissues are now deprived of oxygen and necrosis begins. On the side opposite to the origin of blood supply, small diamond-shaped infarcts develop and finally rupture occurs through these sites. Bacteria may or may not enter the dead tissues, but, as can be seen from Van Zwahlenburg's description, they are not essential. They may augment the changes which already have been initiated.

Van Beuren²² describes this same mechanism as that by which perforation is induced in cases of intestinal obstruction. This sequence of events seems to be well accepted in the case of intestinal obstruction but apparently this knowledge has not been applied in the study of pathogenesis of similar conditions.

Infiltration of tissues by neutrophils is generally credited to bacterial invasion, but this is not necessarily the case. Pepper and Farley¹⁶ state that broken-down tissue in small amounts, may give a marked and early rise in white count. Downey⁸ feels that even in the case of acute appendicitis, there is enough tissue damage to explain the very early leukocytosis. Prochnow¹⁹ showed that leukocytosis with relative increase in neutrophils could be demonstrated postoperatively, even in non-infected hernioplastics. This shows that tissue damage may be responsible and infection need not be present. According to the descriptions of Van Zwahlenburg and Van Beuren, it is easy to see that tissue death is not a late event in the chain.

That slowing of the blood stream is accompanied by extravasation of fluid into the tissues is so well recognized that arguments and examples need not be cited. Van Zwahlenburg^{23a} distended intestinal loops and found that as the blood supply was obstructed, even in a dry atmosphere, drops of fluid appeared on the serosal surface. Downey has shown that venous stasis will cause leukocytic infiltration of tissues, consequently, necrosis of tissues need not precede accumulation of leukocytes.

These inflammatory changes do not follow upon the slow increase in size of a cyst, because the blood supply has an opportunity to accommodate itself to the slowly increasing distention. This is

illustrated in such cases as mucocele of the appendix, where great distention may be present without inflammatory changes.

From the foregoing discussion, it would seem that acute distention of an obstructed hollow viscus is followed by acute inflammatory changes. It remains now to show that this can be demonstrated experimentally.

Material and Method. In the experimental work, dogs were used. The tissue specimens were fixed in formalin and sections stained with hematoxylin and eosin or with Gram-Weigert for bacteria. Smears and cultures were made of tissues and lumen content. Where constant pressure was applied within the lumen of a hollow viscus, the Perusse bottle was used. This apparatus is so arranged as to deliver a constant but adjustable water or air pressure. In some experiments, increased intraluminal pressure was induced by filling the obstructed or normally closed lumen with sterile hypertonic saline or glucose solution.

I. Clinical Material. Within the past few years, several investigators, including Andrews¹ and Westphal,²⁵ have implicated mechanical factors as etiologic agents in appendicitis⁴ and gall-bladder disease. Andrews feels that stones are precipitated by biliary stasis and that once stones begin to form, the pressure-distention mechanism is in full swing. Westphal, in a paper on appendicitis, likens the appendix trying to expel a fecalith to the gall bladder attempting to expel a calculus. He feels that both conditions are in reality dependent on a pressure mechanism. The cystic duct is usually found to be plugged by a stone in cases of acute cholecystitis. This observation is borne out in an unpublished series of cases studied by Zierold.²⁷

1. Clinical Appendicitis. The thesis that acute appendicitis is usually a form of closed loop obstruction rather than a bacterial disease is now being made the subject of an extensive investigation. Though the data cannot yet be published, some of the conclusions reached thus far will be indicated. In 108 cases of appendicitis studied at the Minneapolis General Hospital in 1935, there was an 81% incidence of definite obstruction to the lumen in the acute cases, caused by an impacted fecalith in 60% of the cases. In the perforated cases, the incidence of obstruction rose to 97% and a fecalith was the obstructing mechanism in 81%. These appendices had the pathologic characteristics of closed loop obstruction with all inflammation distal to the point of obstruction. There was marked distention with thinning of the walls and the perforations routinely appeared on the antimesenteric side. Correlated with these findings are the observations that bacteria were found in the tissues in only 12% of the non-gangrenous appendices. In the gangrenous and perforated group, the incidence of bacteria in the tissues rose to 17%. These preliminary reports tend to confirm the impression that the obstructive element is very important and the bacterial element of lesser significance. These results check closely with a

large experimental series and a clinical series from the University Hospital.

That the obstructive mechanism may be of great importance in the causation of appendicitis is not a recent idea and was advocated in 1897 by Pozzi,¹⁸ who accredits the original idea to Dieulafoy. Pozzi stressed the importance of the valve of Gerlach as a factor in converting the appendix into a closed loop. This factor is being investigated by Wangenstein and his coworkers, who find evidence of a sphincter-like mechanism at the base of the appendix. Considerable resistance to the flow of water is almost invariably encountered, pressures of 30 to 60 cm. of water being withstood before water will run into the cecum from the appendix. Such intraluminal pressures, if maintained over a period of hours, will obviously lead to changes in the appendical wall.

Westphal has shown that two other factors operate to convert the appendix into a closed loop. He has demonstrated that the appendical lumen is normally narrower at the base. Thus, fecal masses, laminated by successive layers of secretion, become impacted at the base. The other factor is that the musculature of the appendix is normally heaviest toward the base. He shows by Roentgen ray examinations that appendical peristalsis is ineffectual in the organ, most often beginning at the base and progressing toward the tip.

Banks and Green³ report a case of carcinoma of the cecum in which appendicitis developed. At operation the tumor was found to be obstructing the base of the appendix which was inflamed and distended to the size of a banana. They refer to similar cases reported by Mayer, Shears and Parker and Rosenthal.

2. *Carcinoma of the Sigmoid with Perforation of the Cecum.* In support of the idea that a pressure-distention mechanism is capable of causing intestinal perforation, the following similar cases are briefly outlined. Both patients were elderly men with carcinoma of the sigmoid colon. Each had been given barium by mouth and then was sent to the hospital with a diagnosis of intestinal obstruction of unknown origin. The obstruction was complete in each case and Roentgen rays showed tremendous gaseous distention of the large bowel, especially in the region of the cecum. Both patients expired before operative intervention could be made. In each case, at autopsy, the cecum showed multiple perforations through infarcted areas on the side opposite to the entering blood supply.

The ileocecal valve had remained competent, so that with the obstructing carcinoma the large bowel had become a closed loop. As material accumulated and decomposition continued, the distention became progressively greater. The cecum gradually became deprived of its blood supply by increasing intraluminal pressure. Finally, areas of necrosis appeared and through these infarcts, perforations resulted. The tissues showed a severe inflammatory reaction with dense leukocytic infiltration and areas of necrosis.



FIG. 1.—A clinically gangrenous appendix which illustrates the principles of closed loop obstruction, with distention, thinning and gangrene of the walls, distal to the impacted fecalith. The mucosa is ulcerated and sloughing, while the dilated lumen contains dissolving fecalith, fluid and débris. Proximal to the point of obstruction, the lumen is normal in caliber, the wall is normal in thickness and sections show very slight inflammation. Distally, sections show necrosis with thrombosis of vessels.

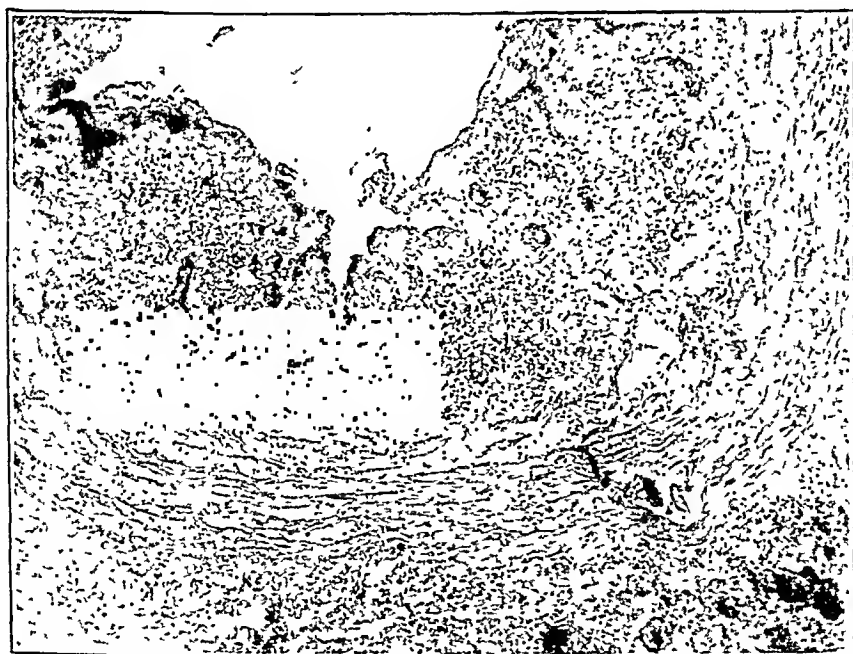


FIG. 2.—Photomicrograph of a dog's ureter after having been subjected to 15 cm. of water pressure for 18 hours. There is edema of the periureteral tissues, marked leukocyte infiltration of all layers, separation of the muscle bundles by distention and inflammatory exudate. The mucosa is necrotic and sloughing. This corresponds closely to the microscopic picture of gangrenous appendicitis.

Gram-Weigert stains showed bacteria on the serosal surface, from the escaped contents but there were no bacteria in the tissues.

Sperling,^{21a} in his paper on competency of the ileocecal sphincter, reports 2 cases in which perforation of the large bowel occurred proximal to the point of obstruction caused by a carcinoma. Koucky¹³ reports a similar case seen at autopsy and the author has operated upon such a case. This "circumscribed meteorism" was first described by Maydl²⁰ in 1883 and Bayer²⁰ in 1889, in which the cecum becomes distended after distal colon obstruction. The development of this phenomenon depends on competency of the ileocecal valve. Kocher¹² in 1889 emphasized that gas pressure in the bowel could cause gangrene and Anschutz²⁰ and von Greyerz²⁰ showed that the thinness of the wall and the relative width of the cecum are the causes of the greater distention in this region. The latter inflated two rubber balloons of unequal size, tied to a T tube, and showed that the larger balloon inflated quickly and burst before the smaller one reached any noteworthy size. In this regard De Quervain²⁰ says, "With membranes of equal elasticity, the pressure is higher when the radius is smaller; therefore, that degree of pressure which will suffice to distend the membrane with the larger diameter, will not suffice for the smaller." Rost²⁰ states that if air is blown into the rectum, patients first complain of pain in the cecum. Von Greyerz and Shimodeira²⁰ have shown that distention of the bowel decreases its arterial blood supply. Gatch, Trusler and Ayers¹⁰ have measured the blood flow through obstructed loops distended by various gas pressures and found that as the pressure was increased, the blood flow decreased. They repeated the observation that the greatest effect is seen on the antimesenteric surface. Dragstedt, Lang and Millet⁹ concluded that distention interferes with the flow of blood in the vessels of the walls of the intestine.

II. *Experimental Data.* In order to understand the pathogenesis of perforation in obstruction, it is necessary to recognize certain fundamentals in bowel physiology. It is known that the normal sustained intraintestinal pressure in dogs is 2 to 4 cm. of water. There are normally 10 to 12 contractions per minute. Sperling^{21b} has shown that simple obstruction doubles the normal intraluminal pressure and with activity of the bowel, this pressure is increased 15 times. He found that a maintained higher pressure gave rhythmic contractions of the same rate but more vigorous in amplitude. The stasis of obstruction not only increases the height of contractions but pyramids the pressure. As the obstructed bowel becomes fatigued, there are intermittent cycles of activity and this explains the colicky type of pain. Sperling also found distention to be an intense stimulus to secretion. This is stressed by Herrin and Meek.¹¹ These observations bear out the ideas of Van Zwahlenburg on the hydraulic vicious cycle. As the fluid pressure increases,

peristaltic and secretory stimulation becomes more intense and this again increases the pressure. Marked changes in absorption also are shown in the obstructed bowel. Sperling demonstrated that absorption is increased up to 40 cm. of water pressure and then decreases. The normal non-distended bowel absorbs 86% of the water placed in it in 1 hour, whereas the obstructed bowel absorbs only 8 to 10%. As the blood supply is cut off by distention, edema occurs and a segment of obstructed bowel increases its weight by 114% in 24 hours, according to Sperling.

1. *Closed Loop Intestinal Obstruction.* In 7 dogs the appendix was severed from the cecum and converted into a closed loop. Some of these loops were full of feces, some empty of gross fecal material and some were washed out with tap water. The specimens were removed at intervals varying from 2 hours to 6 weeks. The empty loops developed acute inflammatory changes only if distention supervened. Both full loops became gangrenous in 48 hours and one perforated. The washed loop, removed after 6 weeks was quite normal. Here we see that, with the same bacteria in all, acute changes were found only when the loop became distended.

In 4 dogs, washed closed loops of ileum were prepared. These were removed in 24 to 72 hours. The early specimens showed marked distention with a hemorrhagic fluid and the 72-hour specimen perforated distally on the antimesenteric border.

In 4 dogs, closed loops of cecum were established. Two were washed and two were full. One full loop perforated in 24 hours and the other was distended and gangrenous in 48 hours. One washed loop was incorrectly prepared, a piece of ileum being incorporated so that it perforated from distention by ileal fluid in 2 weeks. The other washed loop was removed after 6 weeks and was quite distended by gas and fluid but was microscopically normal, probably because the distention had been gradual.

In 2 dogs, closed loops of rectum were made, one full and one empty. The full loop became distended and ruptured the sutures in 5 days; whereas after 6 weeks the empty loop, although distended by gas, was microscopically normal.

From these experiments, several general conclusions can be drawn. 1, the fate of a closed loop is definitely correlated with its location and the function of that segment of bowel. Closed loops of secretory segments regularly distend and rupture whereas absorptive segments become slowly distended by gas and mucus or may remain collapsed. 2, the content of the loop is important in determining the outcome. The contents may act as a hydrophilic agent and cause distention with perforation as will be shown subsequently. 3, the presence of bacteria may cause distention and rupture if they produce fluid and gas by action on the content of the loop. 4, any material in the loop acts as a secretory stimulant. This secretion then augments distention and a vicious cycle is established.

It is seen from these conclusions that bacterial invasion probably is purely secondary to mechanical factors. That the absorption of bacterial products is usually of little significance is shown from the fact that non-distended closed loops show no inflammatory

changes although the lumina contain myriads of living organisms of the same type as those found in distended loops which regularly develop inflammatory changes. Burget, Martzloff, Suekow and Thornton,^{5,6} working with jejunal loops, found that daily aspiration of the loop content allowed the dogs to live indefinitely but without aspiration the loops regularly became distended, gangrenous and perforated. They feel that the organisms in the lumen directly or indirectly cause the formation of fluid. Sperling found that the pressures developed in closed loops may be 20 times the normal. Jejunal loops had 7 times the pressure of ileal loops due to more secretion and showed a consequently greater tendency to perforate. Wilkie^{26a,b} has demonstrated that ileal closed loops containing carbohydrate material routinely perforate but those containing protein material perforate much earlier due to the more active fermentation, liquefaction and gas production. These changes depend on bacterial action but do not indicate a bacterial origin of the perforation.

2. *Experimental Appendicitis.* Wangensteen and Bowers²⁴ have shown that distention seems to be the most important factor in the production of experimental appendicitis. In their pressure experiments, using the Perusse¹⁷ bottle, they routinely obtained acute inflammatory changes, applying pressures ranging from 3 to 30 cm. of water and air for 6 to 18 hours. There was a direct correlation between the degree of pressure and the severity of change; also between the length of time applied and the severity. The incidence of bacteria in the deeper tissue layers also showed a positive correlation with the time and degree of pressure.

It has been generally accepted that appendicitis is caused by increase in virulence of organisms due to stasis in the lumen.²

The following experiments were carried out to test this idea. In 6 dogs, the appendix was washed clean with tap water and then converted into a closed loop distended with brain broth, gelatine, agar, potato, plain broth and Ringer's solution. This should have given the organisms ample opportunity to increase in numbers and virulence without hindrance. These loops were removed after 1 and 2 weeks. In each instance most of the medium had been absorbed. On smear, the lumina contained myriads of organisms of all types. On section, all these appendices showed a subsiding inflammation. On Gram stain, in no instance were there bacteria in the tissues. Since no bacteria were found in the tissues, it was thought that possibly the inflammatory change was on the basis of distention due to hydraulic imbalance. This was investigated as follows. A dog's appendix was converted into a washed closed loop containing a saturated solution of sodium chloride. In 48 hours the entire loop was gangrenous and showed multiple perforations. This experiment was repeated using concentrated glucose with identical results. It was noticed that very few organisms were present and the experiment was repeated but with the addition of gentian violet to the salt and glucose solutions for any bacteriostatic action which it might exert. These appendices were removed in 24 hours and the loops were found to be gangrenous and covered by a fibrinous exudate. The loops contained 5 times as much fluid as was originally injected. In the

loop containing salt and gentian violet there were very rare organisms, while in the loop containing glucose and gentian violet the contents were actually sterile on smear and culture in liver-peptone broth. None of these tissues contained bacteria on staining by the Gram-Weigert method.

These experiments clearly demonstrate that the osmotic pressure may be of more importance than bacteria in causing gangrene and perforation.

Van Zwalenburg^{23a} in 1904 stated that the evident interference with blood supply in appendicitis is best accounted for on the basis of increased intraluminal pressure.

3. *Distention of the Ureter and Renal Pelvis.* The normal upper urinary tract is conceded to be sterile and for this reason it was selected as a suitable site for experiments in acute distention.

In 6 dogs, the peritoneal cavity was opened aseptically and the right ureter was isolated. The ureter was cannulated 6 cm. below the kidney, the cannula pointing toward the renal pelvis. The cannula was then connected to the Perusse bottle. In 2 dogs a pressure of 15 cm. of water was maintained for 6 hours and in 2 others for 18 hours. In 1 dog a pressure of 30 cm. of water was maintained for 6 hours and in another for 18 hours. Only 2 specimens need be described in detail. Fifteen cm. of water pressure for 6 hours produced early gangrenous changes in the kidney pelvis and ureter. Hematuria developed after 2 hours of pressure. The urine was sterile and the tissues showed no bacteria after Gram stain. Water pressure (15 cm.) for 18 hours gave gangrene of the ureter and renal pelvis. Here the picture resembled that of appendicitis, with edema of the periureteral tissues, congestion and hemorrhage in the submucosa, sloughing of the mucosa and dense leukocytic infiltration of all layers. The muscle bundles were pulled apart by the distention and the inflammatory exudate. The urine was sterile and the tissues failed to show the presence of bacteria on Gram stain. This series, while small, shows definitely that acute inflammatory changes may be induced in the sterile ureter and kidney pelvis by increasing the intraluminal pressure. These experiments have no bearing on acute pyelitis nor is it intended to infer that pyelitis is a distention phenomenon (Fig. 2).

4. *Distention of the Urinary Bladder.* The urethra of a male dog was ligated and 500 cc. of Ringer's solution were injected subcutaneously to insure bladder distention. After 24 hours the urinary bladder was tremendously distended, very thin walled and the tissues were so dark as to appear gangrenous. The urine was cultured in liver-peptone broth which after 72 hours showed a sparse growth of Gram positive spore-forming rods. On section, there was relatively little hemorrhage but all of the tissue planes were densely packed with neutrophils. A Gram stain of the tissues failed to reveal the presence of bacteria in the bladder wall.

Creevy,^{7a, b, c} in his work on bladder distention, showed that inflammatory changes regularly followed but hemorrhage was a more pronounced part of the picture in his series. In all of his cases of simple urethral obstruction, the urine remained sterile although acute inflammatory changes accompanied the distention.

5. *Acute Experimental Glaucoma.* The effect of increasing the intraocular tension in dogs by the injection of saline into the globe was investigated as follows, all of the preparations remaining sterile.

In 1 animal the anterior chamber fluid was replaced by sterile normal saline solution, under no increased pressure. The eye was removed after 6 hours and was found to be normal on section. In another eye, the anterior chamber was distended with normal saline for a 6-hour period. Sections showed a dense leukocytic infiltration around the vessels at the angle of the iris and choroid coat. Distention of the anterior and posterior chambers by sterile hypertonic saline for 15 minutes failed to produce inflammatory changes. Distention of the anterior and posterior chambers with hypertonic saline for 6 hours, however, produced dense leukocytic infiltration in the vascular areas of the uveal tract. Similar distention for 24 hours produced the same changes but of a more severe character.

In this series it has been shown that normal saline under no pressure, gives no changes, whereas, by injecting about 1 cc. of saline for the same period, the pressure is increased to a point where inflammatory changes develop. Hypertonic saline caused no changes in 15 minutes but gave a progressively more severe reaction as the experiment was carried on for a longer period and its hydrophilic action was exerted. In no case were bacteria present in these specimens.

Conclusions. 1. The thesis that acute inflammatory changes may develop as a result of mechanical distention of a hollow viscus has been postulated and evidence presented to support it.

2. The sequence of events in the development of acute inflammation has been presented from the standpoint of pathologic physiology.

3. Acute cholecystitis may be based on a pressure-distention mechanism.

4. Our evidence indicates that acute appendicitis is a form of closed loop obstruction in the majority of cases.

5. Two cases of carcinoma of the sigmoid colon with gangrene and perforation of the cecum due to gaseous distention and similar cases have been briefly cited in support of the distention thesis.

6. Experiments on closed loop intestinal obstruction indicate that distention is the important factor in the causation of gangrene and perforation.

7. The importance of the hydraulic vicious cycle in experimental appendicitis has been demonstrated.

8. Experimental maintenance of a constant increased intraluminal pressure will cause acute inflammatory changes in the sterile ureter and kidney pelvis.

9. Severe distention of the urinary bladder of the dog results in acute inflammation.

10. The inflammatory changes of acute experimental glaucoma may be induced by osmotic imbalance.

REFERENCES.

- (1.) Andrews, E.: Arch. Surg., 31, 767, 1935. (2.) Aschoff, L.: Appendicitis: Its Etiology and Pathology, London, Constable & Co., Ltd., 1932. (3.) Banks, A. G., and Green, R. D.: Brit. Med. J., 1, 926, 1935. (4.) Boyd, W.: Surgical Pathology, Philadelphia, W. B. Saunders Company, p. 362, 1929. (5.) Burget,

- G. E., Martzloff, K., Suckow, G., and Thornton, R. C. B.: *Arch. Surg.*, 21, 829, 1930. (6.) Burget, G. E., Martzloff, K. H., Thornton, R. C. B., and Suckow, G. R.: *Arch. Int. Med.*, 47, 593, 1931. (7.) Creevy, C. D.: (a) *Arch. Surg.*, 25, 356, 1932; (b) *Ibid.*, 28, 948, 1934; (c) *Ibid.*, 29, 723, 1934. (8.) Downey, H.: Personal communication. (9.) Dragstedt, C. A., Lang, V. P., and Millet, R. F.: *Arch. Surg.*, 18, 2257, 1929. (10.) Gatch, W. D., Trusler, H. M., and Ayers, K. D.: *Ibid.*, 14, 1215, 1927. (11.) Herrin, R. C., and Meek, W. J.: *Am. J. Physiol.*, 97, 532, 1931. (12.) Kocher: Quoted by Gatch. (13.) Koucky, R.: *Minnesota Gen. Hosp. Bull.*, 4, 269, 1933. (14.) Lanz, O., and Tavel, E.: *Rev. de chir.*, 30, 43, 215, 1904. (15.) Meleney, F. L., Harvey, H. D., and Jern, H. Z.: *Arch. Surg.*, 22, 1, 1931. (16.) Pepper, O. H. P., and Farley, D. L.: *Hematology*, Philadelphia, W. B. Saunders Company, 1933. (17.) Perusse, G. L.: *Surg., Gynec. and Obst.*, 54, 770, 1932. (18.) Pozzi, M. S.: *Presse méd.*, 1, 1, 1897. (19.) Prochnow, F.: *Folia hæmatol.*, 51, 337, 1934. (20.) Rost, F.: *Pathological Physiology of Surgical Diseases*, Philadelphia, P. Blakiston's Son & Co., p. 222, 1923. (21.) Sperling, L.: (a) *Arch. Surg.*, 32, 22, 1936; (b) *Mechanics of Simple Intestinal Obstruction*, Ph.D. Thesis, Univ. of Minnesota (in press). (22.) Van Beuren, F. T.: *Ann. Surg.*, 83, 69, 1926. (23.) Van Zwalenburg, C.: (a) *J. Am. Med. Assn.*, 42, 820, 1904; (b) *Ann. Surg.*, 41, 437, 1905; (c) *Ibid.*, 46, 780, 1907; (d) *Am. J. Surg.*, 18, 101, 1932. (24.) Wangensteen, O. H., and Bowers, W. F.: *An Experimental Study of the Significance of the Obstructive Factor in the Genesis of Acute Appendicitis*, *Arch. Surg.* (to be published). (25.) Westphal, K.: *Deutsch. med. Wchnsch.*, 60, 499, 600, 1934. (26.) Wilkie, D. P. D.: (a) *Brit. Med. J.*, 2, 959, 1914; (b) *Ibid.*, 1, 253, 1931. (27.) Zierold, A. A.: Unpublished data.

THE METABOLISM OF NEPHRECTOMIZED DOGS.

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In order to have a basis for the interpretation of the specific dynamic action of glycine in the nephrectomized dog, it was first necessary to have more complete information on the metabolism of the nephrectomized dog. We believe that by limiting our observations to the first 5 to 6 hours after kidney removal, we have a basis for indirect calculation of the energy production of the kidney, uncomplicated by many of the effects which come about by later accumulation of metabolic end products.

It is generally agreed by those who have made direct measurements of the oxygen consumption of the kidney, that its metabolism is subject to wide variations. (Barcroft and Brodie,^{1a b} Fee and Hemingway,⁵ Hayman and Schmidt,⁷ Van Slyke, Rhoads, Hiller and Alving.¹⁰)

Tangl^{3a} found in 9 dogs that the net decrease in energy metabolism ranged from 3.8 to 14.9% with an average of 8.7%. The *R Q* rose from 0.808 to 0.837. His dogs were curarized. Later,³

using rats, he found by direct calorimetry, a decrease of 8.2%. St. Cserna and Kelemen³ observed a decrease of about 8% in normal animals and in experimental nephritis about 12%. After complete nephrectomy, Dock⁴ found that nephrectomy resulted in an average decrease of about 5% in energy metabolism.

Experimental. All the dogs used were female mongrels, previously fed on a diet of kitchen scraps, and all were fasted 24 hours previous to the experiment.

In most cases a blood sample was taken before the administration of sodium amytal, which was then given intraperitoneally (60 mg. per kg. of body weight). Eight to 10 minutes usually sufficed for complete anesthetization. Small additional doses (50 to 100 mg. per dog) of sodium amytal were sometimes given intravenously whenever needed to preserve the same degree of deep anesthesia.

As soon as the dog was well asleep a catheter was inserted into the bladder, washing carried out and sample discarded. The catheter was left in place until the bladder was again washed just before nephrectomy (2 to 3 hours). The exact time of collection was recorded and sample saved for analysis.

A tracheal cannula was inserted and connected to a Tissot spirometer. Three 30-minute samples of expired air were collected as nearly continuously as possible before nephrectomy and 5 hourly samples were collected after nephrectomy (Series I). In Series II, only 3 samples covering the first 2 hours after nephrectomy were obtained.

Three blood samples, from either the saphenous or external jugular vein, were collected before nephrectomy; the first, before sodium amytal was given; the second, about 1½ hours later; and the third just before the operation. Five consecutive hourly samples were collected following nephrectomy.

Bilateral nephrectomy was performed through an anterior midline incision and the total time consumed varied from 4 to 15 minutes. All precautions to prevent unnecessary trauma and hemorrhage were observed.

Expired air samples were analyzed by means of an accurate Haldane apparatus. The analyses were carefully checked. Heat production was calculated on total *R-Q* since protein metabolism could not be measured after extirpation of the kidneys. Blood and urine urea nitrogen determinations were made by the method of Meyers.⁸

The dogs used in Series II were treated in the same way except their metabolism was followed for only 2 hours following nephrectomy. The 5 control dogs were subjected to the same operation except the kidneys were not removed.

Results. The results of a typical experiment are shown in Table 1. It happens in this case that the sodium amytal was given intravenously in contrast to all other experiments where it was given intraperitoneally. The results are no different. We wish to call attention to the constancy of the basal metabolic determinations, under sodium amytal, both before and after nephrectomy. Urea nitrogen accumulates in the blood, after nephrectomy, at a uniform and constant rate.

Table 2 shows the summarized results on the dogs of Series I at the end of 2 hours after nephrectomy. In order to condense the table somewhat, the blood-urea figures are omitted. The decrease in basal metabolic rate varies from 7.21 to 25.98% of the total

metabolism with an average of 15.17%. In the control animals, treated in the same way except that the kidneys were not removed, the range is from 4.84 to 15.31% with an average of 8.94%. This

TABLE 1.—A TYPICAL EXPERIMENT.

July 10, 1935. Dog. 7. Weight, 7.3 kg.

Sodium amytal intravenously: 8:10, 3.5 cc.; 8:40, 1 cc.; 10:10, 0.5 cc.

	Urine urea N per hr., mg.	Blood urea N, mg. %.			
10:10 Bladder washed			10:38	} 30' sample air	13.15 Cal./hr.
			11:08		
12:20 Bladder washed			11:12	} 30' sample air	13.00 Cal./hr.
			11:42		
12:25	213.8	14.1	11:46	} 30' sample air	13.02 Cal./hr.
			12:16		
12:30 Nephrectomy					
12:43 Kidney wt., 38 gm.					
2:05		18.8	1:00	} 60' sample air	11.55 Cal./hr.
			2:00		
3:05		19.3	2:10	} 50' sample air	10.90 Cal./hr.
			3:00		
4:08		20.2	3:08	} 52' sample air	10.97 Cal./hr.
			4:00		
5:05		23.4	4:11	} 49' sample air	10.60 Cal./hr.
			5:00		
6:15		25.2	5:09	} 60' sample air	11.15 Cal./hr.
			6:09		

TABLE 2.—METABOLISM OF NEPHRECTOMIZED DOGS—SERIES I.

Dog No.	Date.	Wt. of dog, kg.	Average B.M.R. per hr.	Average basal R-Q.	Wt. of kidneys, gm.	Average B.M.R. after nephrec., 2 hrs.	Decrease, %.	Decrease per gm., kidney per hr., Calories.
6	7/3	8.2	15.34	.856	42	12.42	19.0	.070
7	7/10	7.3	13.06	.753	38	11.22	14.1	.048
8	7/12	7.7	12.98	.769	41	10.81	16.8	.053
9	7/16	9.5	18.99	.687	60	16.28	14.3	.015
14	9/6	5.5	10.97	.748	31	9.77	10.9	.038
15	9/9	5.9	13.26	.725	32	10.88	17.9	.075
16	9/16	5.9	13.42	.793	38	10.98	18.2	.064
17	9/18	5.5	9.82	.747	34	9.09	7.4	.021
18	9/20	6.6	13.25	.779	37	12.23	7.7	.028
19	9/23	7.3	13.67	.758	38	11.03	19.3	.070
20	9/27	9.5	18.70	.719	52	15.25	18.4	.066
23	10/7	9.0	15.27	.686	55	11.15	26.0	.075
24	10/11	6.8	14.15	.746	37	13.12	7.2	.028
25	10/14	5.7	12.85	.744	41	11.03	14.2	.044
Av.751			15.2	.052

Controls—Laparotomy Only.

10	7/18	4.5	11.78	.792	36	10.91	7.38	.021
11	7/25	9.1	18.92	.809	..	16.83	11.10	
12	7/30	6.4	11.55	.751	31	10.99	4.84	.015
13	8/1	7.0	9.92	.771	42	9.32	6.05	.014
26	10/15	9.1	12.67	.862	38	10.73	15.31	.051
Av.798			8.94	.026

gives an average net decrease of 6.13%. The decrease expressed in Calories per gram of kidney per hour varies from 0.021 to 0.075 in the nephrectomized dogs and from 0.014 to 0.051 in the control dogs.

Table 3 is really a continuation of Table 2 and is arranged in this manner only to conserve space. In every experiment, except that on Dog 24, the *R-Q* rose. This, we believe to be due to the gradual accumulation of non-volatile acidic substances in the blood and tissues following nephrectomy. The decrease in heat production, expressed both in terms of percentage of the total metabolism and in terms of kidney weight, is somewhat less. This is shown also in the control animals and we believe it to be due to the lesser influence of trauma when studied over the longer period.

TABLE 3.—METABOLISM OF NEPHRECTOMIZED DOGS—SERIES I.

Dog No.	Average of B.M.R. for 5 hrs. after nephrec.	R-Q av. for 5 hrs. after nephrec.	Decrease, %.	Decrease per gm., kidney per hr., Calories.	Blood urea N before nephrec.	Blood urea N at end of 5 hrs.	Urine urea N per hr.
6	13.27	.891	13.5	.049	9.5	16.8	34.7
7	11.03	.849	15.5	.053	14.1	25.2	213.8
8	10.81	.819	16.8	.053	23.8	32.9	229.8
9	17.00	.741	10.5	.033	11.2	19.7	266.5
14	9.83	.819	10.4	.037	10.5	27.3	83.1
15	10.93	.788	17.6	.073	13.6	28.1	93.6
16	11.51	.819	14.2	.050	14.7	19.0	87.8
17	9.42	.816	4.1	.012	25.1	41.0	111.9
18	12.52	.844	5.5	.020	17.6	41.6	106.6
19	11.11	.823	18.7	.067	16.4	27.4	66.3
20	15.80	.758	15.5	.056	8.5	18.8	115.8
23	12.30	.790	19.4	.054	7.3	17.5	44.0
24	12.81	.741	9.5	.036	13.4	27.9	70.2
25	11.24	.771	12.2	.038	9.1	22.5	102.8
Av.805	13.1	.045	13.9	26.1	

Controls—Laparotomy Only.

10	10.82	.823	8.1	.027	20.6	22.5	302.6
11	17.23	.743	8.9	. . .	25.5	17.9	224.7
12	11.10	.832	3.9	.013	13.4	25.3	98.4
13	9.79	.786	1.3	.003	15.8	14.6	36.8
26	11.85	.823	6.5	.019	10.4	11.9	39.4
Av.801	5.8	.016			

The blood urea nitrogen is practically doubled at the end of the 5-hour period. One particularly important point is the lack of parallelism between the decrease in energy metabolism after nephrectomy and the quantity of urea excreted per hour during the control period. This same statement holds true for the experiments recorded in Table 4.

The results of 2-hour experiments on another series of dogs are given in Table 4. In this case, due probably to the shorter time,

the R - Q does not uniformly show a rise. The decreases in energy metabolism are of the same order of magnitude as those given in Table 2. The blood urea nitrogen has increased approximately 50%.

TABLE 4.—METABOLISM OF NEPHRECTOMIZED DOGS—SERIES II.

Dog. No.	Date.	Wt. of dog, kg.	Average B.M.R. per hr.	Basal R - Q .	Wt. kidneys, gm.	Average B.M.R. after nephr.	R - Q after nephr.	Decrease, %.	Decrease per gm. kidney per hr.	Blood urea N before nephr.	Blood urea N after nephr.	Urine urea N per hr., mg.
35	11/5	10.7	18.29	.808	52	15.91	.853	13.0	.045	14.56	17.50	411.6
36	11/6	8.4	14.57	.776	45	12.75	.747	12.5	.040	4.30	7.22	60.2
37	11/7	6.8	13.73	.768	41	12.21	.791	11.1	.037	12.03	13.85	209.9
38	11/8	6.4	14.41	.816	34	11.61	.793	19.0	.081	5.74	7.43	75.7
39	11/11	6.4	13.24	.727	40	11.09	.754	16.2	.054	8.25	11.68	81.3
40	11/12	13.2	19.48	.751	55	17.46	.741	10.3	.037	7.22	14.59	181.6
41	11/13	5.9	10.36	.793	27	8.75	.741	15.5	.060	17.16	22.82	77.6
42	11/19	6.4	13.88	.718	42	12.48	.732	10.1	.033	6.01	7.90	68.6
43	11/20	6.8	12.78	.742	49	11.69	.830	8.5	.022	24.54	29.18	87.5
44	11/21	10.2	18.45	.736	50	15.75	.782	14.6	.054	7.90	13.40	29.8
45	11/22	5.2	9.65	.722	34	8.01	.745	17.0	.048	5.33	8.76	17.7
46	12/10	6.4	12.60	.743	43	10.63	.746	15.6	.016	10.30	14.42	91.8
47	12/11	8.2	17.33	.770	43	14.90	.761	14.0	.057			126.1
48	12/13	8.2	13.83	.711	43	12.26	.807	11.3	.037	7.22	11.33	32.8
49	12/16	7.0	14.28	.751	53	11.91	.777	16.6	.045	6.13	9.14	100.2
50	12/17	6.1	11.41	.733	36	10.14	.734	11.1	.035	5.26	7.91	56.0
51	12/20	8.6	17.79	.712	45	15.47	.755	13.0	.051	7.60	13.61	189.3
52	12/23	6.0	10.31	.730	31	9.53	.755	7.6	.025	7.77	14.28	49.2
53	12/24	5.5	10.30	.745	26	9.92	.801	4.7	.018	13.08	19.74	68.3
54	12/27	7.5	13.56	.721	42	11.58	.707	14.6	.017	9.14	14.46	66.4
55	12/30	6.4	10.11	.777	31	9.18	.759	9.2	.030	9.65	15.30	56.4
Av.				750			.767	12.6	.043	9.50	13.80	

Discussion. Our values for reduction of heat production after nephrectomy are in almost exact agreement with those obtained by Dock⁴ for the rat kidney. However, he did not deduct the decrease due to operation alone as we have done and as we believe necessary in gaining an approximate estimate of the proportion of kidney oxygen consumption to the total consumption of the body. Our results also agree with the higher figures of Barcroft and Brodie^{1a, b} and are somewhat higher than those of Van Slyke and coworkers.¹⁰ Both of these groups of investigators used the more direct method of measuring blood flow and arteriovenous oxygen difference. The fact that our values fall near the same range seems of some significance. It should be emphasized that all who have worked on this problem have found great variations in the metabolism of the kidney.

The values of 4 to 7% of the total metabolism, obtained by

deducting the decrease due to trauma from the decrease after nephrectomy, are a little lower than those of Tangl.^{9a} This may be due to the fact that his animals were curarized instead of anesthetized and the afferent nerves were theoretically functional.

In the 5-hour experiments the $R-Q$ showed a fair rise. This, we believe, indicates gradual elimination of carbon dioxide with the accumulation of non-volatile acids in the blood and tissues. The 2-hour experiments did not show this effect to so great an extent, because the time was so much shorter.

Blood urea nitrogen accumulates at a uniform and constant rate being increased about 50% in 2 hours and 100% in 5 hours. This is in agreement with Bollman, Mann and Magath.² Calculation of the amount of accumulated urea from the increase in blood level and referring it to the amount which should have accumulated according to the basal rate of excretion gave a value which would coincide with equal diffusion throughout about 70% of the body tissues. However, the variation between animals was very great, we have no blood-volume figures at the different times, so we have not considered this figure to be of any significance. We have omitted the calculation from our tables due to lack of space.

There is, apparently, no correlation between the urea excretion of the basal period and the decrease in heat production after nephrectomy. This finding appears to be in contrast to that of Gremels⁶ but confirms Van Slyke and coworkers.¹⁰

Conclusions. After bilateral nephrectomy in the dog:

1. Heat production decreases 3 to 7%.
2. Blood urea nitrogen increases approximately 50% in the first 2 hours after nephrectomy and is doubled in about 5 hours.
3. The decrease in heat production bears no relationship to the amount of urea being excreted during the control period before nephrectomy.
4. The $R-Q$ rises after nephrectomy probably due to the accumulation of non-volatile acids in blood and tissues.

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REFERENCES.

- (1.) Barcroft, J., and Brodie, T. G.: (a) J. Physiol., 32, 8, 1905; (b) 33, 52, 1905.
- (2.) Bollman, J. L., Mann, F. C., and Magath, T. B.: Am. J. Physiol., 69, 371, 1924.
- (3.) Cserna, St., and Kelemen, G.: Biochem. Ztschr., 53, 41, 1913. (4.) Dock, W.: Am. J. Physiol., 97, 117, 1931. (5.) Fee, A. R., and Hemingway, A.: J. Physiol., 65, 100, 1928. (6.) Gremels, H.: Arch. f. exp. Path. u. Pharm., 140, 205, 1929.
- (7.) Hayman, J. M., Jr., and Schmidt, C. F.: Am. J. Physiol., 83, 502, 1928. (8.) Meyers, V. C.: Practical Chemical Analysis of the Blood, 2d ed., St. Louis, The C. V. Mosby Company, 1924. (9.) Tangl, F.: (a) Biochem. Ztschr., 34, 1, 1911; (b) 53, 36, 1913. (10.) Van Slyke, D. D., Rhoads, C. P., Hiller, A., and Alving, A. S.: Am. J. Physiol., 109, 336, 1934.

TUBERCULIN SKIN SENSITIVITY IN CHRONIC TUBERCULOSIS IN THE COURSE OF HOSPITAL TREATMENT.

MEASUREMENT BY STANDARD TUBERCULIN (PURIFIED PROTEIN
DERIVATIVE).

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It is known that in chronic tuberculosis variations in the intensity of the tuberculin reaction occur. In a small proportion of cases the original allergy, or heightened capacity of the tissue to react to tuberculin, gives way to anergy, the condition of complete failure of the tissues to respond. Since tuberculin allergy is such a conspicuous feature of tuberculosis, repeated effort has been made to correlate fluctuations in allergy and the appearance of anergy with the clinical course of the disease.

In general, two theories are applied in explanation of depressed allergy or the appearance of anergy. As far back as 1906, Wassermann¹ referred these states to the development of a specific antibody, "antituberculin," which circulated and neutralized freshly introduced tuberculin. With variation in interpretation, and some disagreement on details, a large German school has adopted this explanation of depressed tuberculin allergy as an antibody phenomenon. According to their view "anergy" of a certain type is a manifestation of immunity. The coincident anergy and clinical arrest which may follow prolonged administration of tuberculin have long been cited as the best evidence for the close relationship of the anergic and the immune state.

Such anergy is commonly termed "positive anergy," in contradistinction to "negative anergy" as exemplified in military tuberculosis and far advanced tuberculosis with cachexia. In the latter states, in the view of the school just cited, the antibodies of the blood and tissues are more than neutralized by the flood of antigen, specifically tuberculin, entering the circulation in severe, progressive tuberculosis.

In this country, on the other hand, there has been a notable tendency in recent years to refer the depressed reactive capacity

following prolonged tuberculin administration, and the anergy of tuberculous pneumonia and miliary tuberculosis, to "desensitization." The chief effort has been not to show that anergy can be explained on the basis of immunity (*i. e.*, the "positive anergy" of the German school), but that immunity can exist in spite of this lack of allergy (see Rich and McCordock,⁹ Derick, Branch and Crane⁴ and Cummings and Delehant³).

Whatever is finally accepted as the underlying explanation for subsidence of allergy in active tuberculosis, it seems important that clinicians be reminded that such subsidence does often occur and that it may be found in tuberculosis both of favorable and unfavorable course.

At the present time there is increasing effort to correlate tuberculin allergy and tuberculous activity. A few of many studies may be cited. Ayman¹ has attempted to find a dosage of tuberculin to which patients with active tuberculosis are positive, and non-tuberculous patients negative. A dilution of 1 to 50,000 of the old tuberculin in his possession seemed to be such a dose, but he freely admitted that severely ill tuberculous patients, with high fever and bronchopneumonic areas in the lungs, were prone to be negative to this dose.

Westwater,¹³ also attempting a quantitative use of the tuberculin test, had some success in correlating types and severity of tuberculosis with skin sensitivity. Massive disease and exudative lesions were found to be associated with low sensitivity, and slight lesions and fibroid tuberculosis with the reverse. The more recent and active the disease the higher the sensitivity. Among patients getting worse on routine treatment, sensitivity remained stationary or diminished, whereas it commonly increased with clinical improvement. Acute excavation was found to be associated with high allergy, whereas a low degree of allergy was found with old cavities. Collapse therapy appeared to reduce sensitivity to tuberculin, and this fact was explained on the ground of desensitization following lymph stasis in the lung.

Neal⁷ noted that a considerable number of patients under pneumothorax treatment, as they improved, became negative to tuberculin, and was led to the conclusion that the tuberculin test might be used as a guide for the termination of pneumothorax treatment. Paretsky,⁸ in following over a thousand cases of positive reactors, saw 80 become negative to tuberculin. Their sensitiveness had decreased from the point where they were sensitive to the customary diagnostic doses of old tuberculin, to the point where they failed to respond to the excessive dose of 10 mg. In every case where loss of tuberculin allergy occurred in what was originally active disease, the disease had become arrested.

Other studies might be cited, but these illustrate the general trend. Most investigations have dealt with the complete disappear-

ance of the tuberculin reaction. A few have been concerned with fluctuations in the intensity of tuberculin sensitiveness. A great difficulty has been in the choice of a suitable method for studying the latter. Variable factors have been the dosage of the tuberculin and the quality of different tuberculin preparations.

The simplest method is to measure the varying size of reaction to a given dose. However, in general the method of serial dilution and determination of the threshold at which reaction occurs, has been found sharper in its results (Schwartz and Heise,¹⁰ Johnston, Howard and Maroney).⁵ The latter method, on the other hand, suffers from cumbersomeness and difficulty in application where a large number of patients are under observation.

Methods of Investigation. The object of the present investigation was to study fluctuations in the level of tuberculin hypersensitiveness in chronic tuberculosis, and correlate them if possible with changes in the clinical course. Since a general impression seems to exist among clinicians that pleural effusion in tuberculosis is followed by reduction in sensitiveness to tuberculin, effort was directed particularly toward the investigation of this problem. Since pleural effusion is a common complication of artificial pneumothorax, it was thought that frequent tuberculin tests in patients under pneumothorax treatment would, in a certain number of cases, through ordinary chance just precede the appearance of a pleural effusion, permitting subsequent study of the fluctuation, if any, in the intensity of the tuberculin reaction.

This investigation differs from previous ones in that standardized tuberculin, *viz.*, the Purified Protein Derivative (PPD),¹¹ was employed throughout. The use of a product of constant strength is obviously necessary in such a study, since small differences in reaction, due to variation in the tuberculin used, might be attributed to fluctuations in the level of the patient's sensitiveness. Another obvious source of error in such a study is individual variance in measuring the size of reactions. The present investigation is subject to criticism on that score, because the actual tests were carried out by a series of workers, each conducting the tests for 3 to 4 months. Actually, however, uniformity in reading and measuring reactions was ensured by uniform training and practice in the Institute, and overlapping periods of several weeks in the hospital as one investigator took the problem over from another. Even with this precaution, in tabulating results, variations in sensitiveness were not looked upon as significant unless they departed by more than 50% from the size of the reaction at the beginning of the study.

The investigation was made on 116 ward patients in the tuberculosis services of Drs. Frank A. Craig and H. W. Hetherington in the Philadelphia General Hospital. Two-thirds (66%) of the group, were classified as far advanced when the study was begun; 24% as moderately advanced and 10% as minimal or suspected tuberculosis.

The plan at the outset was to test a large group once a month with the hope that a considerable number of patients, sufficient for drawing conclusions, would remain under observation for the course of the experiment, which was arbitrarily set at 1 year. However, numerous deaths occurred, and discharges from the hospital, with or against advice, were so many that only 67 remained long enough for what was considered minimal required observation of the trend of tuberculin sensitiveness. This minimum was set at 4 months, permitting 5 monthly tuberculin tests. Of the entire group, 20 received 10 or more monthly tuberculin tests.

Of the 67 patients remaining long enough for satisfactory observation, 34 were under pneumothorax treatment. In most of them the procedure was initiated in the hospital. Since, as already noted, pneumothorax is often complicated at some period in its course by tuberculous pleuritis with effusion, it was believed that considerable opportunity would occur for study of the effect of pleural effusion on the tuberculin reaction. Actually 21 of the 34 patients under pneumothorax treatment developed effusions in the course of treatment. In addition, 3 cases of pleural effusion occurred among the 33 patients not under pneumothorax treatment. A little less than half of the effusions occurred so early in treatment, or at such a long time interval from the next tuberculin test, that their relation to skin sensitiveness seems quite uncertain. In 13 cases, or more than half, however, the time relations of effusion and test were such that it seemed fair to draw conclusions.

It is evident from the previous studies cited that variations in skin sensitivity can best be detected by small doses of tuberculin. As pointed out, patients with progressive or advanced tuberculosis are not highly sensitive to tuberculin, and are in fact much less sensitive than healthy persons in contact with open tuberculosis. Originally it was planned to give all patients in the study 3 tests with the Purified Protein Derivative tuberculin, *viz.*, the standard first dose, the second dose (used in routine testing for those failing to react to the first dose), and a very small dose, one-tenth the size of the small standard first dose, calculated to discover the lower limits of sensitiveness. Actually it proved impossible to gain general consent for the three injections, and in the study, as it was carried to completion, the gross standard second dose was omitted, and only two injections were given each month, *viz.*, the standard first dose of the Purified Protein Derivative (0.00002 mg.), and one-tenth of this amount (0.000002 mg.). This proved a fortunate selection; for in these dilutions the Purified Protein Derivative afforded a delicate indicator of the degree of tuberculin sensitiveness. The lower strength commonly appeared to be the threshold value.

Tuberculin Sensitivity of the Patients Studied. The general level of sensitivity to tuberculin was low. In the entire group of 116 patients there were no strong reactions to 0.00002 mg. of the Purified Protein Derivative. Indeed in the whole group only 2 patients gave reactions consistently averaging more than a two plus reading, *i. e.*, reactions in which the dimensions of the inflammatory swelling exceeded 20 by 20 mm. These patients were among the 47 tested for periods of 4 to 10 months. One was a colored male remaining 9 months and the other a white female tested for 8 months. Of the 20 remaining for 10 months or more not a single one averaged more than a two plus reaction to the stronger of the 2 cases.

Of the 116 patients 8 were negative to the stronger of the chosen doses of the Purified Protein Derivative throughout the whole course of their study. These were not tested with the standard second dose of Purified Protein Derivative (which is 250 times the size of the standard first dose), so that it is impossible to say whether they were tuberculin-negative or not. Experience in other patients has shown that most tuberculous patients negative to the first of the standard doses do respond to the second.⁶

The suitability of the two chosen doses as indicators of the lower limits of tuberculin sensitiveness in the patients of the series is

shown by comparison of the results of testing with the standard first dose of the Purified Protein Derivative and a dose one-tenth this size. Twenty-seven per cent (31 of 116) of the entire group were negative to the first dose (0.00002 mg.) two-thirds of the time, while 72% (83 in 116) were negative to one-tenth of the standard first dose (*i. e.*, to 0.000002 mg.) through two-thirds of the period of testing.

Fluctuation in Sensitiveness to Tuberculin. The 2 cases charted in Table 1 demonstrate the threshold of tuberculin sensitiveness,

TABLE 1.—THRESHOLD AND FLUCTUATION OF SENSITIVENESS TO TUBERCULIN.

Patient, A. P., colored male, aged 15, far advanced tuberculosis, sputum positive for tubercle bacilli.

Patient, M. D., white female, aged 40, moderately advanced tuberculosis, sputum recorded as negative, pleural fluid positive for tubercle bacilli.

Date, 1935.	Size of reaction in millimeters		Size of reaction in millimeters.	
	0.00002 mg. PPD.	0.000002 mg. PPD.	0.00002 mg. PPD.	0.000002 mg. PPD.
May 2	15 x 16 x 1	12 x 11 x 1		
June 14	Omitted	12 x 11 x 1		
July 17	25 x 20 x 2	12 x 10 x 1		
Aug. 15	16 x 14 x 2	11 x 10 x 1	12 x 11 x 1	Neg.
Sept. 4	15 x 13 x 3	12 x 11 x 2	14 x 10 x 2	Neg.
Oct. 6	12 x 11 x 2	Neg.	10 x 5 x 1	7 x 5 x 1
Nov. 7	Trace	Trace	Trace	Trace
Dec. 4	10 x 8 x 1	Trace	8 x 6 x 1	Neg.
1936				
Jan. 7	15 x 14 x 1	10 x 8 x 1	18 x 14 x 1	Neg.
Feb. 5	22 x 20 x 2	14 x 12 x 1	8 x 7 x 1	Neg.
Mar. 10	20 x 20 x 2	13 x 12 x 1	14 x 10 x 1	10 x 8 x 1
Apr. 21	30 x 25 x 2	14 x 12 x 1	10 x 8 x 1	Neg.
	Patient improving		Patient improving	

and may be cited also as examples in the study of fluctuation in sensitivity. The first, A. P., shows a type of curve seen a number of times, in which the intensity of response to tuberculin started at a fairly high level, dropped considerably and finally returned to the original level. In this case, under the standard set, the variation in size of reaction is considered significant. In the other case, M. D., we considered the range in size of reaction for the most part within the limits of experimental error. The threshold is apparent. We have recorded this case as one in which no significant persistent change in the level of sensitiveness occurred. In the October-December period, however, an unmistakable depression of tuberculin sensitivity occurred. It is noteworthy that this was coincident with an acute pulmonary consolidation. This cleared subsequently and in succeeding months this patient improved.

Of the 67 patients studied over a period of 4 months or more, 39, or more than half, maintained approximately the same level of sensitiveness throughout the period of observation. In several of these cases, however, the level was a negative reaction. Twelve of the 20 who were under observation for 10 months to a year maintained the same level of sensitiveness. All of the others fluctuated in the degree of their response to tuberculin.

In the beginning of the experiment it was thought that a seasonal variation in sensitiveness might be found. Actually the largest reactions occurred in many of the patients in the summer of 1935, followed by a lower level in the succeeding months. This might be attributed to seasonal influence, but it is to be noted that the study began in the early summer and that in a large percentage of the patients the clinical course was down hill from the beginning. It is quite possible that the high summer level was merely a reflection of the better clinical condition at the beginning of the study. Schwartz and Heise,¹⁰ it may be noted, were unable to correlate fluctuations with seasonal change.

TABLE 2.—SENSITIVENESS TO TUBERCULIN IN PATIENTS GETTING BETTER AND WORSE.

Date, 1935.	Patient, A. D., white female, aged 25, far advanced tuberculosis, sputum positive for tubercle bacilli.		Patient, M. K., white female, aged 27, far advanced tuberculosis.	
	Size of reaction in millimeters.		Size of reaction in millimeters.	
	0.00002 mg. PPD.	0.000002 mg. PPD.	0.00002 mg. PPD.	0.000002 mg. PPD.
May 2	Listed plus	10 x 9 x 1	Omitted	Neg.
June 14	Omitted	Trace		
July 17	15 x 16 x 3	Neg.	11 x 10 x 1	5 x 5 x 1
Aug. 15	15 x 10 x 1	Neg.	14 x 9 x 1	Neg.
Sept. 4	25 x 20 x 2	14 x 12 x 1	8 x 6 x 1	7 x 7 x 1
Oct. 6	10 x 8 x 1	Trace	18 x 18 x 1	Trace
Nov. 7	Neg.	Neg.	Trace	Neg.
Dec. 4	10 x 10 x 1	Neg.	Trace	Neg.
1936				
Jan. 7	Neg.	Neg.	Neg.	Neg.
Feb. 5	12 x 10 x 1	Trace	Trace	Neg.
Mar. 10	Trace	Neg.	6 x 5 x 1	Neg.
Apr. 21	Neg.	Neg.	Trace	Neg.
	Patient improving		Patient becoming progressively worse	

A continuous drop in sensitiveness occurred as a rule in patients whose disease was becoming steadily worse (*e. g.*, patient M. K., Table 2). Very often the reaction was negative to the doses used for 3 or more months before death. On the other hand, in a still larger number of patients who showed signs of clinical improvement, with loss of fever, slight gain in weight and slight clearing of Roentgen ray evidence of infiltration, a continuous drop in sensitiveness occurred. Patient A. D., Table 2, is an example. This experience may be compared with that reported by Paretsky.⁸ The patients of our series were not shown to be tuberculin negative, as strong doses of tuberculin were not used. Nor did they become arrested, as was the case with Paretsky's patients who became negative. Ours were too far advanced, for the most part, to hope for arrest, but their dropping sensitiveness with improvement might be analogous to the loss of sensitiveness, reported by Paretsky with complete arrest of the disease.

No correlation could be established between patients' temperature and their sensitivity to tuberculin. The majority of patients in the

series were not febrile. A few had temperatures rising as high as 103°. The clinical course in these patients was bad, and in general they did not react to the two doses of tuberculin used. However, several patients who were afebrile and improving also were insensitive to the doses of tuberculin used. Cases were seen in which an increasing sensitiveness to tuberculin coincided with a rise in afternoon temperature, and the reverse was also seen.

The course of tuberculin sensitivity in the 67 patients observed through five or more monthly injections is summarized in Tables 3 and 4.

TABLE 3.—TWENTY TUBERCULOUS PATIENTS RECEIVING MONTHLY TESTS WITH TUBERCULIN FOR 10 OR MORE MONTHS.

Far Advanced Cases (14 Cases)

(Average age 25 yrs., age range 12 to 41 yrs.)

7 maintained an approximately level skin sensitiveness with minor fluctuations; 2 of these were consistently negative to the doses of tuberculin used. Three improved clinically, 1 grew worse and 3 showed no change.

7 decreased steadily in skin sensitiveness. Four of these improved clinically, 2 grew worse, and 1 showed no change.

Moderately Advanced Cases (6 Cases).

(Average age 25 yrs., age range 13 to 31 yrs.)

5 maintained an approximately level skin sensitiveness, with minor fluctuations. Two of these improved clinically, 1 grew worse and 2 showed no change.

1 decreased steadily in skin sensitiveness. No clinical change occurred in this case.

TABLE 4.—FORTY-SEVEN TUBERCULOUS PATIENTS RECEIVING MONTHLY TESTS WITH TUBERCULIN FOR 4 TO 10 MONTHS.

Far Advanced Cases (30 Cases).

8 increased in skin sensitiveness. Five of these improved clinically, 2 grew worse, but with periods of transient improvement, and 1 showed no change.

18 maintained an approximately level skin sensitiveness with minor fluctuations; 5 of these were consistently negative to the doses of tuberculin used.

4 steadily decreased in skin sensitiveness. Three of these grew worse and one showed no change.

Moderately Advanced Cases (11 Cases).

3 increased in skin sensitiveness. Two of these improved clinically, and 1 showed no change.

5 maintained an approximately level skin sensitiveness, with minor fluctuations.

3 steadily decreased in skin sensitiveness. Two of these improved clinically and 1 grew worse.

Minimal or Suspected Cases (6 Cases).

2 increased in skin sensitiveness.

4 maintained an approximately level skin sensitiveness, with minor fluctuations.

A contrast will be noted between Tables 3 and 4 in that 13 or 28% of the patients remaining the short period exhibited a rise in skin sensitiveness as compared with none among the patients remaining the longer period. The explanation lies in part in the composition of the two groups. Those remaining the shorter time were as a group in somewhat better clinical condition, even though the disease was anatomically advanced, and difficult to hold in the hospital.

The rise in sensitiveness of so many of them may reflect some slight improvement in their clinical state.

Fluctuation in Sensitiveness as a Result of Collapse Therapy and Pleural Effusion. In the patients of this series pneumothorax *per se* appeared to have little if any influence on skin sensitivity to tuberculin. *A priori*, explanations could be formulated for either a fall or a rise in general tuberculin skin sensitiveness, for the former on the ground of desensitization by increased absorption of tuberculous matter retained in the non-moving lung, and for the latter on the ground of expulsion of infective material from the collapsed lung, and consequent relief from an already existing desensitizing process. Actually pneumothorax was initiated so gradually that neither of these effects could well be expected. In a number of cases the intensity of the reaction decreased in the months following the induction of pneumothorax, but to no greater degree than in an equal number of patients, without pneumothorax, following a similar clinical course.

This experience, it may be noted in passing, might be compared with that recently reported by Neal,⁷ but no patient in this series improved within the time limit of the study to the extent of arrest, as in Neal's patients who became negative to tuberculin after several months to several years of treatment.

Loss of sensitivity, from sudden excessive absorption of self-manufactured tuberculin and corresponding desensitization might be expected to follow thoracoplasty. "Tuberculin shock" after thoracoplasty has been described (Coryllos).² In our series decrease in the intensity of the tuberculin reaction followed thoracoplasty in 3 out of 4 cases where this operation was performed. In 1 of these cases each of two stages was followed by a slight drop in the intensity of the reaction. The number of cases is obviously too small to permit generalizations.

TABLE 5.—TWENTY-FOUR TUBERCULOUS PATIENTS WITH PLEURAL EFFUSIONS RECEIVING MONTHLY TESTS WITH TUBERCULIN FOR 5 TO 12 MONTHS.

Sequel of Appearance of Fluid.

1 increased in skin sensitiveness.

4 showed no change in skin sensitiveness; in 3 of these the reaction to tuberculin was almost negative both before and after the appearance of the effusion.

8 definitely decreased in sensitiveness.

11 showed no change from which conclusions could be drawn; in these cases fluid was present at the beginning of the study or appeared so long before the next tuberculin test that any immediate effect was considered undiscovered.

The study did, however, afford results on the effect of pleural effusions, which merit some consideration. Table 5 summarizes the course of response to tuberculin in the 24 cases of effusion. As noted, 21 of these were in patients with artificial pneumothorax. Of the 20 patients under observation for approximately 1 year 13 had pleural effusions; in 12 of the 13 the effusion was a complication

of pneumothorax. As the table shows, in the majority of cases permitting conclusions, the advent of tuberculous pleural effusion was followed by a decrease in the intensity of the tuberculin reaction. It is noteworthy that in 1 case the removal of fluid by aspiration was followed by an abrupt change from a negative to a positive reaction.

Thus if any conclusion can be drawn from the series of tuberculin tests in patients whose pulmonary tuberculosis was complicated by effusion, it is that the latter depresses tuberculin sensitivity. Such an effect might be explained on the ground of desensitization from absorption of exudate rich in tuberculo-protein. It should be recalled that pleural effusions are often rich in tubercle bacilli, for the most part enmeshed in the fibrin layer adhering to the pleural surfaces. In the early days of the effusion before appreciable fibrous organization of this fibrin occurs, considerable absorption of autolytic products might take place through the highly vascular pleural membranes. Possibly further collapse of the lung by the exudate might play some rôle.

It must not be forgotten, however, that among the patients suffering pleural effusions were many whose general course was unfavorable, and that among such patients in general many exhibited decreasing sensitivity. It is thus entirely possible that instead of the depression in sensitiveness being related to the effusion, both are to be attributed to progression of the pulmonary disease.

Summary. Fluctuations in the intensity of the tuberculin skin reaction were studied by monthly tests in 116 ward patients with chronic pulmonary tuberculosis. Twenty patients remained under observation approximately 1 year and 67 for more than 4 months. To ensure uniformity, standardized tuberculin (Purified Protein Derivative) was used throughout the experiment. Two doses, *viz.*, 0.00002 mg. (the standard first dose) and 0.000002 mg. (one-tenth of the standard first dose) were employed on each patient. In most cases one or the other of these detected the threshold of reaction.

The general level of sensitiveness to tuberculin was low. Strong reactions were never seen. Of the 20 patients remaining under observation approximately a year not one averaged more than a 2+ reactions to the stronger of the 2 doses. Eight of the 116 patients were negative to both doses for the whole course of their study. To the stronger dose 27% of the entire group were negative, and 72% to the weaker dose, two-thirds of the time.

Of the 67 patients injected at 5 or more monthly intervals, more than half maintained approximately the same level of sensitiveness, as did 12 out of 20 followed for approximately a year. The fluctuations in the remainder were of inconstant character, but certain consistent trends were observed. While, as is already well known, patients with unfavorable course tended to lose their tuberculin sensitiveness as the end approached, a definite continuing depression

of sensitivity was observed also in patients with chronic tuberculosis of long duration, but somewhat favorable course. On the other hand, transient or prolonged increase in sensitiveness occurred in numerous patients with clinical improvement.

Observation was directed particularly toward the effect of special therapeutic procedures employed, and also toward such events as pulmonary spread of the disease, and particularly pleural effusion. Pneumothorax *per se* had no noticeable effect. In the small number of cases of thoracoplasty observed, a drop in sensitivity followed the operation. In the majority of cases pleural effusion appeared to depress skin reactivity.

No correlation could be established between tuberculin skin sensitivity and the patient's temperature or with seasonal influences.

REFERENCES.

- (1.) Ayman, D.: J. Am. Med. Assn., 103, 154, 1934. (2.) Coryllos, P.: Quart. Bull. Sea View Hosp., 1, 337, 1936. (3.) Cummings, D. E., and Delehant, A. B.: Trans. Nat. Tuberc. Assn., 30, 123, 1934. (4.) Derick, C. L., Branch, E. A. G., and Crane, M. P.: Am. Rev. Tuberc., 32, 218, 1935. (5.) Johnston, J. A., Howard, P. J., and Maroney, J.: Ibid., 29, 652, 1934. (6.) Long, E. R., and Seibert, F. B.: Ibid., 35, 281, 1937. (7.) Neal, J. R.: Ibid., 32, 326, 1935. (8.) Paretzky, M.: Ibid., 33, 370, 1936. (9.) Rich, A. R., and McCordock, H. A.: Bull. Johns Hopkins Hosp., 44, 273, 1926. (10.) Schwartz, W. S., and Heise, F. H.: Am. Rev. Tuberc., 24, 479, 1931. (11.) Seibert, F. B.: Ibid., 30, 713, 1934. (12.) Wassermann, A.: München. med. Wchnschr., 53, 2396, 1906. (13.) Westwater, J. S.: Tubercle, 15, 543, 1934.

CONSIDERATIONS AND EXPERIMENTS ON THE HYPERSENSITIVE NATURE OF AMIDOPYRINE AGRANULOCYTOSIS.

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It appears to be definitely proved that the use of amidopyrine alone or combined with various other drugs in some persons causes agranulocytosis (agranulocytic angina, neutropenia maligna or granulo(cyto)penia maligna).

Persons recovered from amidopyrine granulocytopenia react when given a single dose of amidopyrine with several symptoms, the most constant and important of which is a violent fall of the granulocyte count (Madison and Squier⁷; Zinberg, Katzenstein and Wice¹¹; Plum^{8a}; Buus-Hansen and Holten,² etc.). This granulocyte fall cannot be produced by other drugs, and the reaction cannot be produced by amidopyrine in cases recovered from granulocytopenia maligna caused by other agents, *e. g.*, salvarsan (v. Bonsdorff¹). These facts seem to me to be of special value as proofs of the etiologic significance of amidopyrine in granulocytopenia maligna.

The question how and why this very serious effect of amidopyrine is produced in the human organism still remains to be solved. In the

following, I shall endeavor to give a brief outline of our present knowledge, describe a few experiments concerning the question and put forward a hypothesis which I hope may be of value.

It is a fact that a very large number of patients and healthy persons have taken amidopyrine, a great many of these in rather large doses and for a long time without any harm whatever. On the other hand, it must be taken for granted that in quite a number of cases—even if it is only a few as compared with the number having taken amidopyrine—this medication has caused granulopenia. These facts appear to show that there cannot be question of a toxic action of amidopyrine in the same sense as for instance in strychnine causing an acute poisoning or a chronic intoxication or salts of heavy metals causing an intoxication acute or chronic. It seems to be certain that amidopyrine granulopenia arises only in persons hypersensitive to this substance. Hypersensitivity to drugs is often called idiosyncrasy, by which term *sensu strictiori* is meant an abnormal state which is displayed by an increased and altered reactivity to the intake of various drugs. This reactivity is characterized by the appearance of certain morbid phenomena, the idiosyncratic symptoms, which are quite independent of the nature and physiologic action of the substance causing the symptoms. The idiosyncrasy depends on an individual disposition and an exposition, a sensitization of an individual naturally disposed. This sensitization is brought about by a *repeated* dosage of substances liable to cause idiosyncrasy. At first the intake of the drug is not followed by any morbid symptoms, but after a varying number of doses the idiosyncratic phenomena appear. These are rather polymorphic, and in different persons the same agent may cause different symptoms, for example acetosalicylic acid may cause exanthems in one person, asthma in another and edema in a third individual.

The liability to provoke idiosyncratic reactions varies for different substances. It seems to be rather small for phenacetin, greater for the barbiturates, for instance, and Nirvanol (Phenylethylhydantoin) provoke idiosyncratic reactions in about 65% of human beings. Amidopyrine is known to produce idiosyncratic reactions fairly often.

The question arises if granulopenia maligna can be recognized as an idiosyncratic symptom as exanthems, asthma, and so forth. This question cannot be answered definitely but I want to point out that a case of granulopenia maligna caused by the drug Nirvanol just mentioned has been reported by Feer.³ It may be justified to regard the granulopenia in this case as an idiosyncratic symptom as Nirvanol is known to cause such symptoms very often.

It may be mentioned in this connection that leukopenia is a rather common feature in anaphylactic reactions which have much in common with the idiosyncratic reactions. In my opinion, this

tends to show that granulopenia may be regarded as an idiosyncratic phenomenon, and so far there should be no objection against regarding the granulopenia maligna caused by amidopyrine as the result of a sensitization of a naturally disposed individual by the repeated dosage of this drug.

The cases of amidopyrine granulopenia recorded in the literature have arisen after doses extending from a single tablet (in a patient who long ago had got amidopyrine (Zinberg, Katzenstein and Wice¹¹)) to the continued use of the substance for several months (*e. g.*, a case reported by Buus-Hansen and me²). These facts are well in accordance with the concept of granulopenia maligna as an idiosyncratic phenomenon. The time and dosage required to produce idiosyncratic symptoms varies extremely in different individuals. It is well known that a patient may use luminal, for instance, for a long time and then suddenly get skin eruptions; on the other hand, another patient may have an exanthem after only a few doses.

It has also been seen that the granulopenia with accompanying symptoms has not been recognized until 5 days after the last intake of amidopyrine (Case 5, Holten, Nielsen, Trausbøl⁶). This together with the other facts just referred to reminds one very much of the facts relating to cinchophen and hepatitis caused by this drug. Exactly as is the case with amidopyrine, very large numbers of persons have taken cinchophen without any harm even for long periods, but a few have had more or less severe liver damage. The parallel between amidopyrine-granulopenia and cinchophen-hepatitis is in a way stressed by the fact that the danger adhering to the use of the drug was not recognized till several years after the introduction of the substance into therapy. Cinchophen was introduced in 1908 and the cinchophen hepatitis was described in 1923. Amidopyrine was produced in 1893. In Scandinavia, it was used very little until cibalgin (a combination with dial *i. e.*, diallylo-barbituric acid) was introduced in 1925. In 1934, amidopyrine agranulocytosis was recognized in Scandinavia. Like amidopyrine cinchophen produces idiosyncratic reactions fairly often. Quick⁹ thinks it logical to assume that the hepatitis is also an idiosyncratic phenomenon when caused by cinchophen. He calls attention to the Arthus phenomenon, the subcutaneous necrosis produced by subcutaneous injections of heterologous protein after sensitization of animals with this protein. Necrosis or sterile inflammations as idiosyncratic reactions may arise in other places than the skin, *viz.*, in the lungs, kidneys, joints, brain and liver. Quick regards the hepatitis, a sterile inflammation or a necrosis, in cinchophen poisoning as an Arthus phenomenon. One may transfer Quick's hypothesis for cinchophen-hepatitis to granulopenia maligna. The essential pathologic condition here is in the bone marrow where the neutrophils and their mother cells are almost or entirely lacking. This may

be due to a partial necrosis or something near to it of this part of the bone marrow. The erythropoiesis and thrombocytopoiesis is not affected, and it is in good accordance with modern views on bone-marrow function to regard the 3 main functions of the marrow as bound to separate systems.* I believe it to be a fertile working hypothesis to regard the bone-marrow reaction in amidopyrine granulopenia as an Arthus phenomenon localized to the leukopoietic part of the bone marrow. Experimental work along this line is in progress.

Turning now to the experimental work done to elucidate the pathogenesis of amidopyrine granulopenia, I refer again to the experiments in patients recovered from an attack of this disease. A single dose of amidopyrine causes as already mentioned a rapid fall of the leukocyte count lasting for several days. In a few cases (*e. g.*, one of Plum's^{8b} cases) this fall did not occur until a couple of days after the intake of the drug, whereas in the majority of the experiments it comes after $\frac{1}{2}$ to 1 hour. The retardation of the reaction has its parallel in serum sickness, where some symptoms do not arise until after several days after the serum injection.

It is well worth adding that Plum^{8b} has shown that the amount of polynuclear cells in the bone marrow, as shown by sternal puncture, decreases rapidly and for a long time in experiments of this kind. This very clearly shows that the changes produced take place in the bone marrow and are not limited to the peripheral blood.

The view has been advanced that the granulopenia maligna from amidopyrine was due to some unknown impurity of the drug and in support of this view it has been stated that all cases of amidopyrine granulopenia reported were produced not by the original Pyramidon Bayer but by substitutes. This view, however, will not hold as Kloster⁶ has reported a case after Pyramidon Bayer which recovered and was tested with Bayer's preparation and showed the typical severe leukocyte drop.

The attempt to produce granulopenia in animal experiments has not had great success. Madison and Squier⁷ had one rabbit out of 18 which got granulopenia, and Hoffman, Hickey and Butt⁴ reported some experiments (without stating definite dates), where the experimental animals had large falls of leukocyte counts after very large doses of amidopyrine. My coworkers Nielsen and Transbøl and I⁵ have given amidopyrine to 26 rabbits and 2 guinea pigs. The doses varied from 2.5 to 250 mg. per day, and the animals were treated for 30 to 90 days, in several cases intermittent dosage was tried. Leukocyte counts including differential counts were made with intervals from 1 day to 1 week. In no case could definite leukopenia be seen. The leukocyte count varies—from 4500 to 16,000. The granulocyte count varies from 30% to about 80%.

* For histologic descriptions of the bone marrow in granulopenia maligna, see Holten, Nielsen and Transbøl, *loc. cit.*

Of course, one must be very cautious in concluding that amidopyrine dosage has produced leukopenia. As an example showing this very clearly I quote an experiment:

Guinea pig.

Feb. 7.	Leukocytes, 11,900.	Neutrophils, 81%.
2.5 mg. amidopyrine by mouth from Feb. 7 until March 11. Leukocytes counted 6 times: 7450 to 14,800. Neutrophils, 30 to 70%.		
March 12, 13 and 14, no amidopyrine was given.		
March 15, 10 mg.; on March 16, 17 and 18, nothing was given.		
March 17:	Leukocytes, 4500 with 54% neutrophils.	
March 18:	Leukocytes, 12,500 with 58% neutrophils.	
March 19:	Leukocytes, 16,000 with 44% neutrophils; 10 mg. amidopyrine.	
March 20:	Leukocytes, 13,100 with 66% neutrophils.	
March 21:	Leukocytes, 12,700 with 47% neutrophils.	
March 22:	Leukocytes, 14,300 with 30% neutrophils; 20 mg. amidopyrine.	
March 23:	Leukocytes, 10,600 with 45% neutrophils; 20 mg. amidopyrine.	
March 24:	Leukocytes, 12,500 with 58% neutrophils; 20 mg. amidopyrine.	
March 28:	Leukocytes, 15,500 with 71% neutrophils; 20 mg. amidopyrine.	

On March 17 we thought we had produced leukopenia, but the subsequent course did not confirm this belief. The drop was probably only a spontaneous variation.

On the whole, I believe one must say that animal experiments have hitherto given no certain evidence and have not contributed to the solution of the problems. However, if it is assumed that the granulopenia is an idiosyncratic reaction one cannot wonder at this. Such reactions cannot be produced with the same frequency and under similar forms in different species, and man seems to be more predisposed than any other.

Experiments have been briefly published tending to show that bone-marrow changes could be found in animals given amidopyrine without any demonstrable changes in the peripheral blood. Until details are published, I believe it wise to consider this with some reservation.

We have made some experiments to prove the idiosyncratic nature of amidopyrine granulopenia in man by trying to transfer the idiocyncrasy passively. Serum from a case of amidopyrine granulopenia drawn under sterile precautions was injected intracutaneously in 2 healthy individuals. No hyperemia or any other sign of hypersensitivity appeared after 24 hours. The injection of amidopyrine solution (and a couple of other substances for control) at the points of serum injection produced no local or universal symptoms whatever. This means that the "reagins" are not to be found in the circulating blood or that the substance producing idiosyncrasy is not amidopyrine but amidopyrine which has undergone some alteration or other in the human organism.

In a patient in whom hypersensitivity to amidopyrine had previously been proved,² serum from a healthy person who 1 hour before had taken 300 mg. amidopyrine was injected intracutaneously; as a control serum drawn previous to the intake was also injected. No

local or universal reaction whatever occurred. Hence we did not succeed in showing skin hypersensitivity to serum containing amidopyrine in a person proved to be hypersensitive to amidopyrine when taken by mouth.

Squier and Madison¹⁰ have been able to demonstrate cutaneous hypersensitivity in convalescents from amidopyrine granulopenia by placing patches of linen with a suspension of amidopyrine on the skin. Buus-Hansen and I² have not been able to confirm this in our hypersensitive patient, but the patient had a slight but certain drop of her leukocyte count.

Summary. 1. It can be stated as definitely proved that amidopyrine can cause granulopenia maligna.

2. The mechanism of this is not known but it is not similar to the common toxic action of drugs. An individual hypersensitivity appears to be necessary; this hypersensitivity may be produced after a very short or a very long use of amidopyrine.

3. Parallels between amidopyrine-granulopenia and cinchophen-hepatitis are drawn. It is suggested that granulopenia may be caused by a kind of Arthus phenomenon in the bone marrow.

4. The author and his coworkers have failed to produce granulopenia in animal experiments.

5. We have likewise not been able to transfer "amidopyrine allergy" passively.

REFERENCES.

- (1.) von Bonsdorff, B.: Finska Läkaresällsk. Handl., 76, 1072, 1934. (2.) Buus-Hansen, A., and Holten, C.: *Lancet*, 2, 1342, 1935. (3.) Feer, E.: *Monatshefte f. Kinderheilk.*, 42, 157, 1929. (4.) Hoffman, A. M., Hickey, N. G., and Butt, E. M.: *J. Am. Med. Assn.*, 102, 1137, 1934. (5.) Holten, C., Nielsen, H. E., and Transbøl, H.: *Ugeskrift f. Læger*, 96, 155, 916, 1934; *Acta med. Scand.*, 84, 45, 1934. (6.) Kloster, J.: *Norsk. Mag. f. Lægevidensk.*, 97, 25, 1936. (7.) Madison, F. W., and Squier, T. L.: *J. Am. Med. Assn.*, 102, 755, 1934. (8.) Plum, P.: (a) *Ugeskrift f. Læger*, 96, 916, 1934; (b) 98, 91, 1936. (9.) Quick, A. J.: *Am. J. Med. Sci.*, 187, 115, 1934. (10.) Squier, T. L., and Madison, F. W.: *Wisconsin Med. J.*, 34, 175, 1935. (11.) Zinberg, I. S., Katzenstein, L., and Wice, L. E.: *J. Am. Med. Assn.*, 102, 2098, 1934.

THE GENERAL HOSPITAL; ITS PSYCHIATRIC NEEDS AND THE OPPORTUNITIES IT OFFERS FOR PSYCHIATRIC TEACHING.

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It has been variously reported that personality disorders (*i. e.*, psychiatric problems) constitute anywhere from 35 to 75% of the case load of the general practitioner. Insofar as the author has been able to learn, these figures, though probably they are fairly

* A part of the Department of Psychiatry, Colorado University School of Medicine, financed by the Rockefeller Foundation.

accurate, are estimates not based on any statistical studies. Certainly the significant importance of the frequency in occurrence of such disorders, in general hospital and general medical practice, is rapidly coming to the fore as indicated by the ever increasing number of publications dealing with the topic.

One of the objectives of our Psychiatric Liaison Department,* organized September, 1934, has been to determine the frequency with which psychiatric problems occur in the average general hospital and dispensary patient population, to develop workable procedures for studying and treating these problems, and to evaluate, in general, the opportunities offered by the general hospital and dispensary for acquainting the medical student and intern with the diagnosis and treatment and possible prevention of such reactions

Scope of Report. This report deals simply with statistical studies concerning the frequency of occurrence of such disorders in a general hospital and dispensary patient clientèle; and, with the opportunities offered by such a clinical organization as the general hospital for preparing the medical student and intern for the adequate and economical management of such patient problems as will come to them in the general practice of medicine. Our statistics are based on the patients admitted to the Colorado General Hospital Dispensary between September 14, 1934, and September 1, 1935 (*i. e.*, 11½ months), and on the admissions to the wards of the Colorado General Hospital between September 15, 1934, and March 30, 1936 (*i. e.*, 17½ months).

Basis of Statistics. This analysis is made on the statistics as recorded by the "record"† organization of the hospital and on those kept by the Psychiatric Liaison Department. Any patient seen for the first time in any of the 18 clinics of the outpatient dispensary was regarded as a "new" case. Thereafter, such a case visiting the clinic was regarded as an "old" one. In the outpatient department the psychiatrist only examined patients referred by these clinics. A patient seen only once in some other department before being referred for psychiatric study was considered "new." The only exception was made in the instance of the medical clinic referrals. In that clinic, because there were but few physicians to handle the very large case load, on an average of 5 visits were required of the patient before all of the complete studies desired by that unit for diagnosis could be made. Therefore, a "new" case referred to the psychiatrist from the medical clinic connotated a case seen in that clinic not more than five times and referred as soon as the medical examination was finished. Any other patients referred to the psychiatrist were considered "old" cases.

All patients admitted to the wards of the hospital were either "new" cases or those temporarily "away on leave." The latter were not considered new admissions when returning for further hospitalization. Thus the delineations made in regard to new and old cases, in the instance of the dispensary patients, were not necessary when considering those coming to the hospital proper.

Incidence of Psychiatric Problems in the Outpatient Department. During the 11½ months' period, 9792 "new" cases came to the dis-

* Billings, E. G.: J. Am. Med. Assn., 107, 635, 1936.

† The author wishes to thank Miss Margaret Neale, Director of the Record Room, and Mrs. Della Smith, formerly supervisor of the Outpatient Department of the Colorado General Hospital, for their assistance in compiling the statistics.

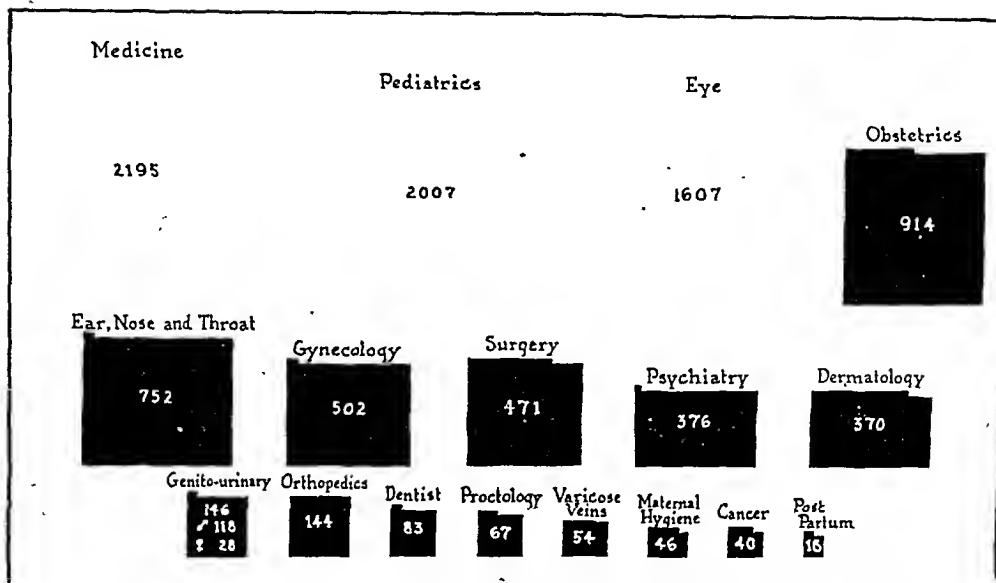
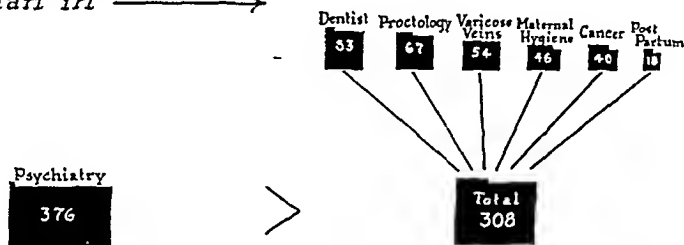


FIG. 1.—Relative teaching importance of dispensary clinics in Colorado General Hospital based on number of new cases admitted to each during year 1934-1935.

More New Cases
Seen in
Dispensary Psychiatry
than in →



Equals as many cases as:

- $\frac{1}{6}$ of new admissions to Medical clinic
- $\frac{3}{4}$ of new admissions to Surgery clinic
- $\frac{3}{4}$ of new admissions to Gynecology clinic
- $2\frac{1}{2}$ times number of new admissions to either Orthopedic or Genito-urinary clinics.

dispensary. Of these, 376 patients (3.83%, or 1 out of every 28 admissions) were referred for psychiatric study after their initial examination. (There were also referred 299 "old" cases which are mentioned here only because the total of "old" and "new" cases examined psychiatrically is utilized in an analysis of the referring source to be discussed later.) When the "new" cases admitted to each of the 18 clinics of the dispensary and the "new" cases referred to the psychiatrist are separately and graphically plotted (Fig. 1), the block of psychiatric material as found in the dispensary stands eighth in the series. As relatively viewed in another way, there were more "new" cases seen by the liaison psychiatrist, in the outpatient department, than were seen in dentistry, proctology, varicose-vein clinic and post-partum clinic combined (Fig. 2). These psychiatric cases in number approximately equaled: $\frac{1}{6}$ of the new admissions to the medical clinic; $\frac{3}{4}$ to the surgical clinic; $\frac{3}{4}$ to the gynecology clinic, and $2\frac{1}{2}$ times the number admitted to either the orthopedic or genitourinary clinics.

There were in all ("old" and "new") 675 cases referred to the psychiatrist by 12 of the 18 departments. The majority (70.2%) were so relegated by the medical clinic (Table 1).

TABLE 1.—SOURCE OF 675 CASES ("OLD" AND "NEW") REFERRED TO THE PSYCHIATRIST BY THE DISPENSARY.

(Adults, 565; Children, 110; Males, 261; Females, 414.)

Per cent.	Clinic.
70.2	Medical
15.7	Pediatric
2.9	Gynecology
2.1	Dermatology
2.1	Pre-Clinic
1.7	Neurology
1.7	Eye
1.2	Ear, Nose, Throat
0.8	Admission office
0.4	Surgical
0.4	Genitourinary
0.4	Laboratory
Total 99.6	12 clinics (of a total of 18)

Based on our statistics, 14.6% of all new cases admitted to the medical clinic (about 1 out of every 7) were deemed preëminently psychiatric problems requiring treatment such as could only be given by a physician *with considerable psychiatric training*. Through close collaboration with the resident internists, studies of the "new" case material entering this medical clinic revealed nearly as many more cases which presented clinical problems that could not be understood and properly treated by a physician without *some* medicopsychiatric experience and training.

Incidence of Psychiatric Problems on the General Hospital Wards. During a period of $17\frac{1}{2}$ months (September 13, 1934, to March 30,

1936), there were admitted to the wards of the Colorado General Hospital a total of 6442 patients. These included 3347 women (1075 obstetrical cases), 1996 men and 1099 children. Of this number, 228 patients, 134 women, 77 men and 17 children (3.54% of the total, or 1 out of every 28 admissions), were regarded as psychiatric problems by the regular non-psychiatric visiting staff and were referred to the Psychiatric Liaison Department. These figures do not include the more *minor* personal maladjustments and personality reactions to and concomitant with admission to hospital, operation, child birth and the various somatic disease syndromes. However, we feel that these figures *do* represent the incidence of cases coming to this general hospital *that require the services of a physician well trained in psychiatric examination and therapeutic procedures*. For more detailed statistics showing the number of admissions to each hospital service, the number of psychiatric referrals therefrom, and the percentage of admissions so considered, see Table 2.

TABLE 2.—ANALYSIS OF SOURCE AND INCIDENCE PER HOSPITAL SERVICE.

Total admission to Colorado General Hospital (Sept. 13, 1934, to March 30, 1936) = 6442.		Of these there were referred to the Psychiatrist 228 cases, or 3.54% (i. e., approx. 1 of every 28 admissions).	
General Hospital service or ward.	No. of admissions.	No. of cases referred to Psychiatrist.	Percentage of admissions referred to Psychiatrist.
1. Female medicine	1194	100	8.3
2. Male medicine	1016	63	6.2
3. Female surgery	1078	23	2.1
4. Male surgery	980	14	1.4
5. Obstetrics	1075	11	1.02
6. Pediatrics	1099	17	1.5
Total	6442	228	—

Some Psychiatric Needs of the General Hospital and Four Points in Argument for Developing a Psychiatric Service Therein. If the tradition is true that a large percentage of the dispensary "medical shoppers" and "chronics" and patients readmitted to the general hospital for diagnostic studies are psychiatric problems, then the above statistics speak, without further ado, for the existence of a very pertinent and economically important need the general hospital has for a psychiatric service within its confines.

Aside from this, there is a still more important need that the general hospital has for developing facilities adequate to the understanding and treatment of the patient as a "mentally integrated whole." This need is connotated in the requirement that the teaching hospital promote medical research. Psychiatric research is increasingly calling upon the general physicians and specialists for assistance in understanding the "whole man." Conversely, the internist, surgeon or child research physician, who is endeavoring to arrive at the same understanding from a more traditional beginning,

is feeling a greater need for the psychiatrist's collaboration. The general hospital is certainly at present one of the most generally acceptable meeting places for all concerned in fulfilling an intention of this nature. Since it would seem that collaborative research of this bent is notably reliant on the advisability and possibility of the ingrowth of psychiatry in many general hospitals, the question then that makes itself immediately felt is—what psychiatric material is offered by the general hospital, and can the average general hospital afford a psychiatric development within its bounds? To answer this issue, four prerequisites must be considered: 1, A reasonable cross section of psychiatric material must be available; 2, the average accessibility of the personality of the cases for investigation must be conducive to adequate study; 3, a situation in which the concerted thought and coöperation of the various psychiatrists and non-psychiatrists is available for work with the case material; and, 4, a cost of operation of such a project not too great for the average medical school and general hospital.

1. *Type of Psychiatric Material Found in a General Hospital.* The general hospital offers an excellent cross section of psychiatric material as shown by the fact that of the first 745 cases examined and treated, nearly one-half (43.06 to 44.29%) manifested major psychotic disorders, over one-third (34.06%) showed psychoneurotic reactions of all types, and between one-sixth and one-seventh of the malbehavior was understandable, to a great extent, in terms of constitutional factors (Fig. 3).

2. *Accessibility of the Patients' Personalities to Investigation.* Irrespective of diagnosis, the peak of the age level curve of the General Hospital and Dispensary psychiatric patients is 21 to 30 years, whereas that of the patients in the Psychopathic Hospital is 31 to 40 years (Fig. 4). It might be inferred, therefore, that on the whole, the general hospital cases because of age are more plastic and therefore more accessible to psychiatric investigation and therapy. Then, too, and even more important, the psychiatric problems, on the whole, encountered in general hospital are qualitatively the same as found in the formal psychiatric clinic but are in our experience quantitatively less profound and incapacitating to the patient. It is, therefore, possible to study the patient more frequently in his "normal" habitat and surroundings; and to study and understand the fundamental behavior and functioning of the sick person, without as many interfering and misleading secondary features as go with an intensification of the disorder.

In our practice we see either the majority of the patients recover, remain in their respective reactions or get worse within a month, whereas in the identical but quantitatively more profound reactions usually found in psychopathic hospital, the time is measured in at least two to four times this term. Naturally, it would then seem, as in any other "experiment," that much can be learned, with a

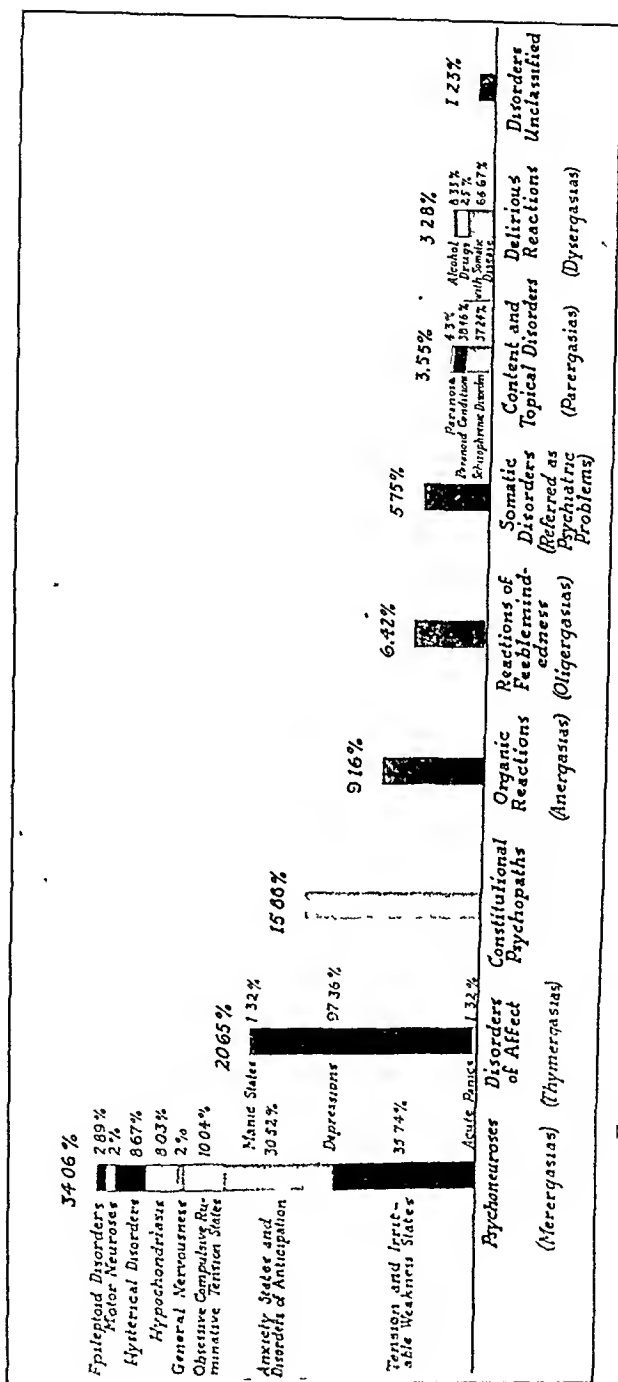


FIG. 3.—Percentage comparison of "Reaction Types" manifested by the first 745 cases.

Note that incidence curve peak on General Hospital falls between ages 21 to 30 while that in Psychopathic Hospital occurs between ages 31 to 40.

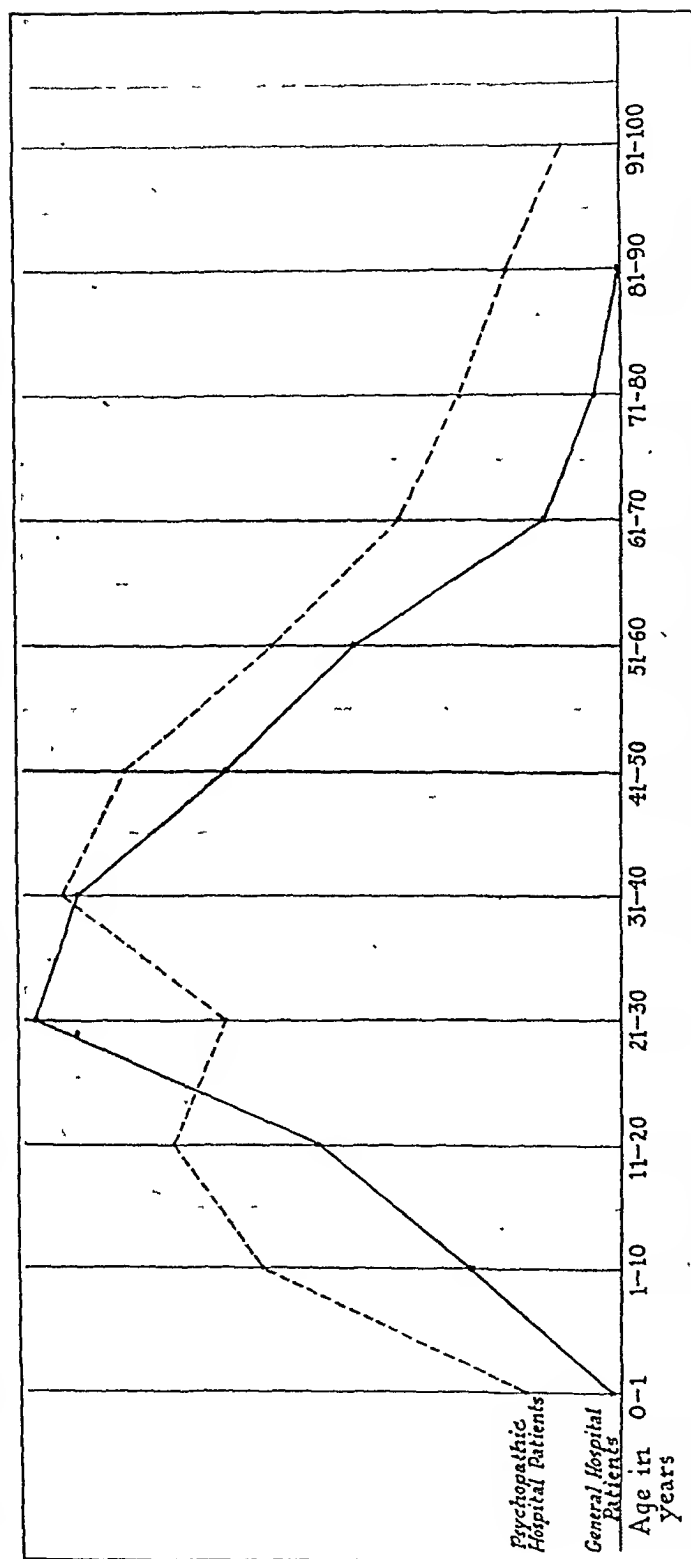


Fig. 4.—Relative age of Psychiatric cases examined and treated in Colorado General Hospital Wards and Dispensary (745) as compared with that of cases examined and treated in Colorado Psychopathic Hospital Wards and Dispensary (2266) from September 1934 to March 1, 1936.

minimum of time expenditure and floundering, from the psychiatric problems found in the general medical-surgical hospital. If a psychiatric hospital or clinic exists in conjunction with the general hospital, as is the case at the University of Colorado Medical Center, experience of undoubted value is offered the post-graduate psychiatric student or fellow, not only in understanding many of the psychiatric problems confronting us in psychiatry, but in practical training in the management of what would be considered office practice.

3. *The General Hospital; A Situation Conducive to the Collaborative Work of Psychiatrists and Non-psychiatrists.* The third item, the opportunity to work with case material hospitalized long enough to allow for concentrated research activity, is, at least in our situation to date, the most difficult one of all to attain. We have spent a great deal of time, and anticipate spending a great deal more, in leading the clinicians, the laboratory, and, most difficult of all, the people and governmental powers to realize that the admission and discharge rules of the hospital, the ordinary investigative and research studies of patients, must be broadened to encompass the problems of the "whole" man or woman or child admitted to the hospital or clinic. Research worth anything to medicine as a whole cannot be pulled out of a "cocked hat" by any one person. It must be the fruition of the combined efforts of all workers in all branches of medicine in a given institutional unit to satisfy the appetites whetted by the communal common sense understanding of the views and objectives of the others of the group. In this hospital and medical school aspirations of this nature are already gradually beginning to appear. We have every reason to believe that this attitude will gather intensity in our institution; and, that it can be developed in *any* general hospital.

4. *Operation Cost of a Department of Psychiatry in a General Hospital.* Finally, the value of such liaison developmental projects to psychiatry must depend ultimately on the formation of more such endeavors; and, therefore, on the financial outlay and running expenses necessary for a general hospital to maintain such a department. This item can be answered in one sentence. It cost the University of Colorado approximately \$338 to furnish two unused laboratories as offices for the Department; and, excepting the salaries, the Psychiatric Liaison Department's expenses have averaged \$28.85 per month.

Summary. 1. In a study of the "new" admissions to the outpatient department and to the wards of the Colorado General Hospital it has been shown that: (a) at least 1 out of every 28 admissions requires the services of a physician *well* trained in psychiatric diagnosis and treatment procedures.

(b) Of the new cases seen in the outpatient medical clinic, approximately 1 out of every 7 (14.6%) are predominantly psychia-

tric problems and as many more require psychiatric understanding and guidance.

(c) Between 6.2 and 8.3% of the admissions (about 1 out of every 13 admissions) to the medical wards of the general hospital conspicuously presented personality disorders which were the explanation of their disabilities.

2. The psychiatric needs of the general hospital are discussed as being, through their fulfillment, conducive to economy and better research along the lines of "physiology of the mentally integrated individual."

3. Four points are elucidated in favor of the development of psychiatric facilities within *more* general hospitals.

FREQUENT PSYCHIATRIC COMPLICATIONS IN GENERAL PRACTICE.*

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THROUGH the gratifying increase of interest in psychiatric problems, much that is valuable has been written on this subject and has become a part of the common fund of medical information. The practising physician encounters far too many psychiatric problems in his daily work to permit him to refer all of them to the specialist in mental disorders, nor is this necessary or desirable for many of the more common problems to be discussed. We believe that a planned study of the personality factors involved in psychiatric disorders greatly enhances the likelihood of successful therapy, although we all know of highly gifted clinicians who deal more or less successfully with many of them without this aid. Everyone agrees that emotional, social, situational and kindred factors may cause complications in any somatic illness, but without some systematic knowledge it is difficult to deal efficiently with the mass of facts accumulated by investigation. As an aid to the practitioner or specialist in other fields we recommend the outlines for investigation of the past history, the family situation and heredity, the origin and development of the present illness, the underlying personality of the patient and the specific symptoms and signs of the various reaction types which may be found in any of the standard textbooks of psychiatry.⁵ In this presentation I shall confine myself to a few of the psychiatric disorders most commonly encountered in the general practice of medicine.

Depression. One of the most common psychiatric disturbances seen is that of depression, which composes approximately 10% of

* Read before the Kansas City Academy of Medicine, Kansas City, Mo., November 20, 1936.

the cases admitted to the hospital (Colorado Psychopathic), and 20% of the cases seen by the Psychiatric Liaison Department (Colorado General Hospital). By depressions we mean those changes in mood varying from slight feelings of discouragement, sadness, futility, "the blues," to the major affective disorders which constitute separate clinical entities; involuntional melancholia, endogenous depression associated with arteriosclerosis, manic-depressive psychoses, psychoneurotic depressions, and depressions in reaction to situations such as death of a loved one, financial loss, illness, personal defeats, or long continued stress and strain. We are all acquainted with the manifestations of the slightly depressed mood; with increased depression we see a growing aversion to activity, a stooped posture and dejected facial expression with wrinkled brow and drooping mouth. Spontaneity of speech is lost, the tone of voice is low and replies to questions are condensed as much as possible. Ordinary movements are performed only with heightened effort and more slowly than is usual. Answers to questions are delayed. The patient likes to be left alone, and expresses in various ways that he is downhearted, miserable, different from other people, lacks interest and is unable to think or act in the customary manner. He may complain of headache, dullness, confusion and inability to think, as well as of constipation and other gastro-intestinal complaints, insomnia (especially of the early-morning-waking-type which is very characteristic of this disorder), and loss of taste and appetite. Vague generalized somatic complaints referable to all organ systems suggest the presence of somatic delusions. In severe cases the patient will complain of feeling unreal or floating away, and of disordered function of various organs. If such delusions are present it is important that an expert consulting opinion be obtained, for a serious schizophrenic reaction may be ushered in by an initial depression with vague hypochondriacal complaints. In contrast to the toxic-organic disorders which are to be discussed later, we find that the sensorium of the depressive is only affected by the retardation. He is usually well oriented for time, place, person and situation; memory, retention and recall, counting and calculation, reading and current knowledge are not intrinsically impaired. Study of the complaint often suggests some degree of insight on the part of the patient. At times the depth of the delusions interferes markedly with judgment, as when ideas of personal wrong-doing, unworthiness, self-accusation, etc., are prominent. Paranoid delusional trends may be present. Often the mood is one of "impure" depression, *i. e.*, mixed with feelings of perplexity, irritability, petulance and suspiciousness. The most common admixture is that of apprehension with depression. Feelings of restlessness, tenseness, being under a strain, and uneasiness are indicative of a state of "tension." Tension, depression and anxiety are frequent concomitants of somatic disease and should be

treated by the practitioner with the same care that he devotes to the primary organic disease.

Before discussing details of treatment an extremely important topic must be considered, that of the prevention of suicide. It is the obligation of every physician to watch for it and to employ preventive measures. Any patient with depressive tendencies should be regarded as a suicidal risk. Dr. Ruth Fairbanks,³ at the suggestion of Dr. Adolf Meyer at Phipp's Clinic, made an investigation of 100 cases who attempted suicide and found that 73% were depressives; while paranoid states, psychopathic personality, general paresis, epilepsy, chronic invalidism and recurrent manic excitement were represented by comparatively small ratios. A study of the case histories showed that the apparent motive for the suicidal attempt in a majority of the cases was a feeling of frustration or failure. A fear of insanity was often prominent, especially in cases in which there was a family history of mental illness. The frequent occurrence of suicides, depressions and alcoholism in the family histories was given special mention by the author. The attempt to escape from delusional persecution as well as from intolerable life situations were motives in a considerable number of these cases. The following danger signals may give the physician hints of a potential suicidal attempt: when the patient shows a definite tendency to self-condemnation and expresses feelings of futility, talks about the burden he is to his family and friends, desires to make a will, or desires to "get out of it all," the physician should employ special precautions such as having someone in constant attendance, removing all sharp instruments, medicines and drugs, and as far as possible ropes, cords, etc. Previous attempts are to be regarded as serious indicators since it has been shown statistically that such patients are especially dangerous, in spite of the myth that unsuccessful attempts are prophylactic. A patient, who is obviously tense, restless, worrisome, who attempts to pull away from attendants, or who shows overeagerness to join in activities outside of the house should be carefully watched. This can best be done in hospitals which are prepared to take care of such problems. An inexperienced personnel is totally inadequate to cope with the cleverness of a determined suicide. The physician in charge must employ special caution in determining when close surveillance should be relaxed. This is a very difficult question since treatment demands that restrictions should be as few as possible to avoid unnecessary rebellion on the part of the patient, and that occupational and other interests should be stimulated. Yet it is well known that many patients commit suicide during the convalescent period when there is every reason to believe that they are improving. Occasionally it seems as if a depressed patient will decide upon suicide and having made the decision is freed from many worries and therefore appears to be recovering rapidly.

The experienced physician will not be deluded by this too rapid change and will increase rather than decrease his vigilance. The special care of suicidal patients is a fascinating problem, and at the present time there is a growing body of informative literature on the subject. The persevering physician will be well rewarded for his pains, since affective disorders usually improve.

The decision as to whether a given patient should be treated as a potential suicide is not only most difficult but of the greatest importance. Many depressed neurotic patients consider or even speak of suicide by way of "escape," without seriously contemplating it. Here the physician must assume some responsibility in minimizing suicide-preventive measures, as their unnecessary use will seriously handicap the patient's recovery.

In general, whether a patient is suffering from a depressed mood secondary to another disorder or whether there is a "true" depression present, the patient should be placed in the most neutral environment possible, and protected against such annoyances as would increase the depression. Visits should be limited and carefully observed, since relatives often make futile attempts to cheer up the patient, or deliver very ill-considered and harmful advice on how to "snap out of it." Exhortations and arguments are especially to be avoided. Only short, cheerful, reassuring visiting should be allowed. In acute phases the physical surroundings should be as comfortable, quiet and non-stimulating as possible, in order to guard against the formation of delusions. Probing or investigative psychotherapy should be avoided. Interviews with the physician should be limited to short visits during which the patient should be made to feel that all his questions will be answered and that his illness is thoroughly understood. Very simple reassurance that mood disorders run their course and that the concomitant physical complaints are only a part of the emotional state is the foundation stone upon which the psychotherapy is built. As far as circumstances and the patient's intelligence permit, he should be cautiously "re-educated" as to his mental state and the damage of recurrences thereby diminished. As the patient shows increasing responsiveness to those talks, the range of activity should be increased in keeping with the abilities of the patient. It is important to remember that increasing privileges too rapidly, premature transfer from a comparatively neutral environment to a more stimulating one, or sudden withdrawal of sedatives without first tapering down the dose may cause the patient to relapse. A depressed patient is extremely critical of himself, and if he is encouraged to do more than he is able he will condemn himself for his failure, confirming the strong self-depreciatory trends already present. The danger of "probing" interviews, or the obtaining of "confessions" by strong urging has been mentioned; an insecure person may react with panic or resentment if the physician insists on penetrating his defense. In the latter

case, the patient may need a transfer of physicians in order to carry on the therapy. The tactful physician will encourage spontaneous discussions with the patient, utilizing the patient's initiative and interest as much as possible and avoiding painful or tabooed subjects until the depression clears up sufficiently to permit investigation. The material covered in these short reassuring interviews should be noted by the physician in order that it may be employed in future reconstruction of the development of the illness. The patient often gives extremely valuable leads to the sources of his preoccupation if the physician is willing to listen. Implicit in the patient-physician relationship is a mutual exchange; the patient gives his trust and confidence in the hope of receiving help; the physician should return reassurance and constructive formulations which will help the patient to meet his problems better from day to day. It is futile to attempt too much at one time since the depressed patient cannot appreciate his assets and will overemphasize his liabilities. With the lifting of the depressed mood, the physician can gradually introduce the topics of etiologic importance and begin such causal therapy as seems necessary or desirable.

The question of when to hospitalize the depressed patient is a highly individual one. Many mild depressions are being successfully handled through office interviews all over the country. The physician must realize his responsibility, however, and insist upon hospitalization 1, when he detects a potential suicide, 2, when the patient's environment mitigates against recovery, 3, when the patient is in danger of establishing a narrow, stereotyped behavior pattern (so-called "rut" formation), and 4, when the patient becomes a severe nursing problem requiring special attention to safeguard his health.

In the hospital, the activities of a patient can naturally be much better controlled than at home. In both places, however, monotony, fatigue and too great expectations are to be avoided. Since the rhythm of a depression varies, the patient may be encouraged by allowing him to do more on the days when he is feeling better, but these rhythms must be carefully explained in advance so that the patient will not be unduly discouraged when he finds himself unable to live up to yesterday's performance. He should be reassured, during the depressed periods, of eventful recovery. We find that walks, easy handicraft projects, reading of extremely light fiction, and superficial conversation are desirable for the more depressed periods. Card games, chess, dancing, athletic games of all types including lawn tennis, golf, croquet and the indoor competitive games can be utilized for the less depressed periods. Naturally the preferences of the individual patient are consulted in planning his daily activity. Rest periods should be provided but the patient should not be allowed to increase these without supervision, since ruminations are fostered by solitary inactivity.

Depressive patients and their relatives often ask the doctor about the value of travel. Patients in a "rut" formation may benefit by a change of scene; but, in general, experience shows that the depressed patient is accompanied by his illness regardless of his surroundings. The physician must have the courage to stand out against such suggestions and recommend real treatment. On the other hand, it must be recognized that under favorable conditions of companionship, finances and the patient's temperament or improving course, change of scene may prove to be a valuable therapeutic aid.

Close attention must be given to the physiologic functions of eating, digestion, elimination and sleep. Weight charts should be kept; nutrition may be maintained by urging the patient to eat or by employing spoon-feeding if necessary. Tonics for the stimulation of the appetite may be employed. Mild cathartics and laxatives are preferable to enemas since the latter may encourage preoccupation. Depressed patients often have an accompanying sleep difficulty usually of the early-morning-waking-type. A warm sedative tub of 1 to 2 hours' duration in the evening is often helpful in relieving this condition. If tension phenomena accompany the depression, small doses of barbital given at those times throughout the day when the tension and depression are at their height are a great aid. We have found barbital, gr. 1, to gr. $2\frac{1}{2}$ given 2 to 4 times a day very useful, although other barbituric acid derivatives may be substituted. Larger doses may lead to dullness, headaches and other subjective symptoms which add to the patient's confusion and feelings of inadequacy. Paraldehyde is excellent for immediate effect, but its vile taste and the prolonged odor surrounding the patient makes it impractical for the treatment of mild depressions. We do not encourage the use of bromides since uncontrolled ingestion leads to toxicity, especially in patients with systemic damage. It is often necessary to explain in detail to patients that the medicines being given them are not narcotics, and will not cause true addiction with the well-known withdrawal symptoms. We keep in mind, however, that there is a very real "psychic dependence" which is seen in those people with personality disorders who are helped to escape disagreeable realities by the use of a drug. Chronic alcoholism may be cited as an example of this condition. The physician is responsible for the complications following the use of drugs prescribed by him. He should recognize the toxic symptoms accompanying prolonged usage or overdosage. To aid physicians in their effort to prevent self-medication we believe that all these drugs should be sold only on a physician's prescription. Some states have laws regulating the sale of such drugs, but much more public education is necessary in order to obtain complete control.

Drugs are best administered in capsules, so that the identity and amounts are concealed and can be changed without comment from the patient. The dosage should be reduced frequently in a consistent

attempt to make the patient independent of his "crutch." It is desirable that patients who are in the hospital be independent of sedative medication before they are discharged.

My time is too short to discuss many other special treatment problems in connection with the depressions. If the principles laid down are utilized to the best advantage, the practitioner will find that he is able to handle these cases with more assurance and with greater success.

Anxiety. The group of symptoms composing the so-called "anxiety syndrome" was first described and named by Hecker in 1893, but was not generally recognized in this country until after the war. It has been known by many misleading terms such as: "disordered action of the heart," "D.A.H.," "irritable heart," "nervous heart," "effort syndrome," "soldier's heart," "neuro-circulatory asthenia," and "functional cardiovascular disorder."

The picture presented varies in the number, character and intensity of the subjective and objective symptoms, according to the underlying personality structure of the patient. Naturally the manifestations of anxiety will be different in a psychoneurotic anxiety state than in an "anxiety state" which merely colors an underlying depressive or schizophrenic reaction. The basic disorder may also be due to brain destruction from head injury, paresis or arteriosclerosis. The anxiety may be associated with, although not directly caused by, some physical disease such as tuberculosis, diabetes or pernicious anemia. It always occurs in an individual who is inclined to be tense and uneasy, with rather sudden transient attacks varying in duration from a few seconds to an hour, and associated with palpitation, precordial discomfort, perspiration, difficulty in breathing, weakness, giddiness and even fainting. Although the symptoms mentioned obviously suggest disease of the various systems the physician can elicit the presence of the anxiety, *i. e.*, a fear of danger from within, a fear of illness or death, or only a feeling of uneasiness or impending danger. Through further questioning he will obtain information regarding difficulty in sleeping, anorexia, easy fatigue, or headache, often of the "band around the head" variety. We also find that the patient may be irritable, restless, losing weight, not feeling fit, or worried without knowing what about or why. A subjective feeling of being cold and unable to warm up is fairly frequent. Direct examination reveals ordinarily a tense, restless, uneasy, apprehensive person with cold clammy hands and feet, dry mouth, and labile pulse and blood pressure which are normal when the patient is asleep. The heart tends to hyperactivity with an occasional extrasystole, the colon may be tender to palpation, and the muscle and tendon reflexes frequently are hyperactive. In the series mentioned this syndrome occurs most often between the age of 21 to 25 and 36 to 40 years. The following table, worked out by Dr. Billings of the Psychiatric Liaison De-

partment of the University of Colorado School of Medicine and Hospitals, will be of value in differentiating between hyperthyroidism and the "anxiety syndrome"¹ (Table 1).

TABLE 1.—A FEW DIFFERENTIATIONS BETWEEN HYPERTHYROIDISM AND ANXIETY.*

Symptoms and signs.	Hyperthyroidism.	Anxiety states.
I. <i>Subjective symptoms.</i>		
1. Thermal response	Heat intolerance	Cold intolerance.
2. Drive and energy	{ Drive 4+ } Easily { Energy 4+ } exhausted	{ Drive 1+ } Constant { Energy 0 } fatigue.
3. Appetite	Increased	Decreased.
II. <i>Objective signs.</i>		
1. Weight	Initial gain; loss	No gain; loss.
2. Motility	Fine tremor	Coarse tremor.
3. Skin	Velvety and warm	Cool and moist.
4. Pulse rate	90 or more	Variable; usually less than 90; normal when at ease or asleep.
5. Pulse pressure	Increased†	No change.
6. Heat production	Increased	Usually normal.
7. B.M.R.	Constantly +20 or more	Erratic; usually normal.
8. Blood cholesterol	Decreased (normal 200)	Normal.

* Prepared by Edward G. Billings, M.D., Colorado General Hospital.

† Due to fall of diastolic pressure.

In treating a patient with an "anxiety syndrome" it is important to avoid the pitfalls of telling him that he should stop worrying, or that nothing is wrong, since he is unable to stop thinking about his trouble, and knows quite definitely that something is wrong. Neither is it profitable to say that the heart is in good condition and imply that it is not by giving advice regarding exercises or prescribing tonics. Pseudo-explanations, such as saying that the precordial sensations are due to gas in the stomach pressing up the diaphragm and crowding the heart, are also to be avoided, for any suggested treatment which does not deal with the actual etiology of the disorder will cause the patient to wander about seeking help, or discourage him further and thereby increase his depression, hypochondriasis and invalidism. The physician must be prepared to spend sufficient time to be sure of the diagnosis and of the actual development of the illness in that particular patient. This demand discourages some physicians since they feel that this procedure is too time-consuming. If, however, one balances the hour and a half required for a systematic examination, which will facilitate and shorten subsequent treatment interviews, against the many hours wasted in discouraging glandular and sedative medication, it will be seen that the long initial interview is entirely worthwhile. The anxiety and associated symptoms must be thought of as an expression of dysfunction of the whole person, and treatment should be directed against those factors which are the cause. Painsstaking effort should be made to rule out any possible physical disease by taking a careful history, making a complete physical and laboratory examination, and studying the possibilities in the differential diag-

nosis. Then the environmental factors are examined. If, by changing occupation or home situation one can relieve the distress, it is obvious that these steps should be taken. If the cause is rooted in some malfunction of the personality, the complaints are studied in great detail in relation to the person who offers them. The serial picture obtained by intimate acquaintance with the patient's problems, assets, liabilities, and goals suggest specific treatment measures for that individual. The general types of these measures are known as aëration or ventilation, suggestion, reassurance, desensitization, and reëducation.

A few useful sedatives and hypnotic drugs should be discreetly employed only as a "crutch" along with other adjuncts (hydrotherapy, packs, and exercise) to help establish *rappor*t and to break the vicious cycle of fears. As in depressions with tension, we have found that barbital in doses of 1 to 2 grs. given 2 or 3 times daily, is the most useful drug. Spastic constipation will be improved by *Tr. belladonna* (minims v-xii, t.i.d.), together with a regular diet and mineral oil. Hydrotherapy is extremely useful for relaxation and improves muscle and skin tone and general metabolism. It may consist of neutral tubs of 1 hour's duration given twice a day, or shower-baths employing both warm and cold water at varying pressures, or cold wet packs.

It is important to remember that psychotherapy begins with the entrance of the patient into the doctor's office. The long initial interview usually has a decidedly beneficial therapeutic effect, because it instils confidence in the patient and points out definitely the prospect of relief. Much of the ease with which a case will

be relieved is due to the fact that the patient gains of himself. With adequate examination and explanation the majority of anxious patients will usually be able to see the real nature of their illness. If the physician will explain the relation of the symptoms to the underlying fears by giving common examples of visceral participation in emotional states such as anger, fright, or excitement, the patient will not concentrate his complaint upon the palpitation, precordial distress, shortness of breath, weakness, and so on. These symptoms become understandable manifestations of emotions which are common to all humanity. They are not disregarded as "imaginary" and therefore not respectable. When explained in a rational manner as the natural physiologic concomitants of an emotional state they lose their ominous significance as the possible forerunners of a dreaded "insanity." The diarrhea of soldiers during an attack; the polyuria during contests or examinations; the palpitation, perspiration, and choking, at sudden fright are common examples.

In view of the complexity of a patient's personality and his experiences it will usually be found that multiple factors are re-

sponsible for his illness. Situational factors dominant in the production of the illness must be altered if possible. Frequently, however, the patient must be taught to accept inevitable handicaps to modify his attitude toward them so that they are not active sources of conflict. He should be kept at his regular work if possible. When necessary the aid of the family should be enlisted, so that detrimental barriers to treatment may be removed. If the patient is unduly concerned or insecure about his work, it may be helpful to explain the nature of his illness to the employer so that the latter may lend sympathetic assistance. "Anxiety states" are eminently treatable, and the simple measures outlined above, when used with foresight and persistence, bring about a recovery in the great majority of cases.

Toxic-organic Reactions. Although in a series of cases seen at the Colorado General Hospital and Dispensary by the Psychiatric Liaison Department (Dr. E. G. Billings) the percentage of delirious reactions including those due to alcohol, drugs and somatic diseases was only 3.3%, there is reason to believe that the general practitioner sees a goodly number of them. The disorders complicating other diseases have received many names such as *symptomatic psychoses*, the *toxic-organic reactions*, the *exogenous reaction types*, the *dysergastic reaction types* (A. Meyer), and *mental symptoms in somatic ailments* (C. M. Campbell).

The delirious reactions are characterized by disorientation, hallucinations and a predominating affect of fear; they are closely connected with somatic conditions in that they are dependent upon, or associated with, intoxications by drugs or poisons, nutritional disturbances, circulatory phenomena and metabolic disorders. These disturbances produce temporary brain changes which are in the nature of edema or the obscure concomitants of fever and acidosis. The occurrence of delirium should not be considered merely incidental to the principal disease picture. It is a complication that may, and in a great percentage of cases does, interfere with the treatment of the presenting clinical problem. To say the least, it increases the suffering, prolongs the duration of the illness, and may necessitate special hospitalization of the patient; it may even be a disorganizing factor of such magnitude as to produce chronic invalidism and incompetency. The delirious patient, befuddled, disoriented, hearing threatening voices, misinterpreting situations, overwhelmed by misgivings and fear and given to action, is in acute danger of injuring himself and even of losing his life by jumping from a window. A very large percentage of deliria either are preventable or can be ameliorated if recognized early.

The delirious reactions are characterized by:

- 1, Clouding of consciousness and drowsiness; 2, Partial or complete disorientation leading to a state of bewilderment; 3, Dream-like or nightmare-like imaginative experiences when awake, with a tendency

to misinterpret the situation in keeping with the haziness and fearfulness; 4, Occurrence of vivid hallucinations and illusions of sight, hearing, tactile sensibility and position; 5, Frequently changing position; 6, Affect of fear and suspicion.

Etiologically the deliria may be grouped as follows:

1, Those due to exogenous toxins or poisons such as alcohol, opiates, bromides, barbiturates, and so on; 2, Those due to chronic cachectic states; 3, Those due to malnutrition, deficiency diseases (pellagra, avitaminosis, and so on) and metabolic disorders (hyperthyroidism, uremia, exhaustion states); 4, Those occurring as a part of an "organic reaction" such as in paresis or cerebral arteriosclerosis.

The general facts relative to a delirious reaction, as elicited on indirect examination (history of the illness from all sources), reveal that the onset of the condition usually is quite sudden and frequently makes its appearance at night, or when the patient's surroundings are changed. This onset is characterized by objective evidence that the patient is misinterpreting sounds, conditions and occurrences in his environment, has dream-like fancies and hallucinations and is partially or completely disoriented. The hallucinations usually are vivid and most frequently involve vision and hearing, although the skin may also be involved. If the above-mentioned features are not foremost, then the restlessness of the patient, his tendency to leave his bed and wander away and his reaction of annoyance, irritation, or fright may signal the beginning of such a reaction.

It can be seen from the foregoing that the treatment of the toxic psychoses requires knowledge of the whole domain of general medicine. Naturally, the specific therapeutic measures will be dictated by the type of infection or poisoning which is the basis of the psychosis. There are, however, certain general principles, which are applicable in the majority of cases:

1, Careful eliminative procedures are fundamental. Among these are catharsis, colonic irrigations, gastric lavage, attention to the fluid balance of the body and urinary excretion, and promotion of elimination *via* the skin.

2, An attempt should be made to control infection, if it is present and to eliminate foci of infection. Surgery often is required for the removal of infection and for the treatment of hyperthyroidism. Roentgen ray and radium may also prove of value. The administration of serums and vaccines may help to secure immunity against various infectious states.

3, The efficiency of the "support systems" should be bettered. For instance, cardiac stimulants and regulators should be utilized in case of actual or even threatened cardiac decompensation.

4, Dehydration and acidosis must be minimized and controlled. Routine dietetic and tonic treatment is required in the management

of the majority of psychoses of this group. Transfusions are indicated if the hemoglobin value is below 50%. They are extremely valuable and may be life-saving in hemorrhage, shock, certain poisonings, especially carbon monoxide, infectious diseases and severe secondary anemias.

5, If cerebral edema is present, spinal drainage and the cautious intravenous administration of hypertonic solutions, preferably 5% saline or 50% glucose, are indicated.

6, Sedation and its proper application with full appreciation of its dangers is important. Sedatives are of value in that they enable the patient to rest, but they should never be given for the sake of convenience in nursing care. Hydrotherapy and/or chemical sedation may be employed.

Of the hydrotherapeutic measures, the most helpful is the continuous or neutral tub. The temperature of the water should range from 97.6° (in case of hyperpyrexia) to 99° F. Care must be taken to keep the temperature in the tub room constant. The patient may be kept in a continuous tub for 1 to 24 hours without difficulty. The time element is solely dependent on the effect desired and the patient's physical status. The delirious patient's vegetative nervous system usually is unstable during his acute illness, and, therefore, shocks in the form of cold water must be avoided. Packs usually are contraindicated because the restraint involved promotes fear.

No hypnotic drugs should be given the patient during the day, but they are permissible at night when he is more apt to be disturbed. The type of hypnotic used depends on the type of delirium and the toxic agent causing the disorder. In general, a quickly acting, rapidly metabolized and rapidly eliminated drug, such as sodium amytal or paraldehyde is indicated. The hypnotic should be given in a large enough dose to cause sleep and should be administered before darkness, since the latter is prone to increase the patient's disorientation and fear. In beginning deliria, continuous sedation for a short time is helpful in preventing a prolonged reaction.

7, The nursing care is worthy of a great deal of careful consideration and requires understanding, ingenuity and skill. The patient must continually be reassured as to the intentions of the nurses and physicians. Furthermore, the management of the environment with the elimination of disconcerting shadows, sounds, and movements is necessary for the comfort and progress of the patient. He should be safeguarded from accident and suicide during the acute manifestations of the psychosis.

8, The verbal productions of the acutely ill patient may be of the greatest value in effecting an adequate personality adjustment, when the acute episode is past, and, therefore, should be noted carefully. This is particularly important in the deliria due to drug and alcohol addiction. In these cases, some analysis of the personality with

subsequent attempts at rebuilding is the only basic way of preventing recurrences.

9, All measures directed toward improving general hygiene are important. A regular daily schedule, written out and strictly adhered to, is useful, and as far as physical condition will permit, exercise and diversions (indoor and outdoor) should be arranged.

10, In many cases psychotherapy, as previously outlined, will prove the most potent of all therapeutic aids.

11, A prolonged period of convalescence is of great importance in preventing late sequelæ of the acute infections.

12, Follow-up care is essential.

13, Prevention is mentioned last although it should be first in the mind of the physician. Usually a medical man is not called until the delirium is present. A surgeon, however, often has it within his power to take steps to avoid a delirium. Apart from the avoidance of unnecessary and unwise administration of drugs, he must take into consideration the emotional factors involved in any surgical procedure. Dr. J. M. T. Finney of Baltimore, Maryland, speaking of "The Obligations and Responsibilities of the Surgeon,"⁴ is an able exponent of the psychobiologic point of view in surgery. He reminds the surgeon that he should identify himself with the patient and remember that the fear, physical discomfort and pain, loss of consciousness, loss of time from one's regular occupation, may all combine "to cause the prospective patient many anxious moments and in certain cases, such an acute state of nervous shock and mental distress as seriously to affect the outcome of the operation."

The Organic Reaction Types. Among the many psychiatric problems encountered by the general practitioner, the organic reaction types are the most readily understandable. In almost all of these conditions, a definite organic lesion is present, and this lesion, if recognized, gives the physician a tangible explanation for the accompanying personality changes. In general, the organic reactions are chronic, being dependent on focal or diffuse, more or less permanent and intrinsic changes in the central nervous system. Obviously, transition states may exist between the delirious and the organic reaction types. Etiologically, the latter are associated with organic toxins, metabolic disturbances, syphilis, arteriosclerosis, neoplasm, trauma, senility, certain epilepsies, eclampsia and organic residuals of meningitis and encephalitis. While the clinical picture varies from case to case, and the etiology and duration of the diseases differ, the characteristic features of this type of disorder may be summarized as follows:

1, A definite organic change exists in the central nervous system. This may be in the nature of nutritional disturbance, neoplasm, inflammation, or degeneration. The motor and sensory reflexes are often disturbed, and these disturbances may lead to derangements of speech and equilibrium and to difficulty in writing and walking. Special laboratory and clinical procedures, such as study

of eye grounds and visual fields, examination of the spinal fluid and encephalography, are of value in diagnosing these conditions.

2, Personality changes are striking and are reflected both in the deterioration of ethical feelings and in the development of behavior patterns inconsistent with the individual's former habits. For example, a respectable person may become vulgar and obscene, and a frugal, conservative individual, extravagant and grandiose. On the other hand, the symptoms may represent an accentuation of the normal constitutional make-up. Thus, paranoid forms of senile deterioration may develop in persons who have always been suspicious and distrustful, and paresis may have a depressed or manic coloring, somewhat in accord with the patient's previous reaction pattern.

3, The affect is characterized by emotional instability with marked fluctuations in the mood. Thus, the individual may exhibit almost mercurial changes from joy to sorrow and back again.

4, Mental changes are quite characteristic and result in a decline in the patient's business and intellectual efficiency. The individual characteristically shows periods of confusion and bewilderment, difficulty in relating events which he has observed, fluctuations in his level of attention, defects in orientation, and retention, impairment of memory and comprehension, marked disturbance of judgment, and even delirium.

5, A large percentage of these conditions is entirely preventable. While this is obviously true in the case of the toxic organic types, it is equally true of most of the organic reaction types, especially all forms of central nervous system syphilis.

6, The prognosis varies according to the reaction types, but it is, in general, poor.

The recognition and treatment of these disorders is a part of the body of common medical knowledge and need not be further elaborated upon here².

By treating the patient as a human being rather than as a defective machine, the individual doctor will be rendering service which will reflect additional credit upon the medical profession. With the increased teaching of psychiatry in the better medical schools we can soon hope that every physician will become aware of the wealth of psychiatric problems in general medicine. We welcome the prospect of a closer union between psychiatry and general medicine for the mutual benefits of such a relationship will improve the standards of medical practice. It is with this thought in mind that the discussion of these disorders has been offered.

REFERENCES.

- (1.) Billings, E. G.: Personal communication. (2.) Ebaugh, F. G.: *The Toxic Organic Reaction Types*, Oxford Medicine, New York, Oxford Univ. Press, vol. 7, 1936. (3.) Fairbanks, R. E.: *J. Am. Med. Assn.*, 98, 1711, 1933. (4.) Finney, J. M. T.: *South. Med. J.*, 26, 180, 1933. (5.) Strecker, E. A., and Ebaugh, F. G.: *Practical Clinical Psychiatry*, 4th ed., Philadelphia, P. Blakiston's Son & Co., Inc., 1935.

THE IMPORTANCE OF SOFT TISSUE LESIONS IN ARTHRITIS.

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THE usual cursory examination of the joints and periarticular structures in arthritis has resulted in an overvaluation of Roentgen ray findings. Routine roentgenograms, however, give details only of bone structure. Shadows of the soft tissues are, at best, poorly registered. Therefore they are usually disregarded and the diagnosis is based solely on the changes in bony articular structures.

The danger of such misinterpretation is realized if we consider that the finding of spurs is commonly accepted as evidence for the presence of osteoarthritis (hypertrophic arthritis). It was long ago pointed out by pathologists (Weichselbaum, Pommer, Schmorl) and recently confirmed by Keefer³ and his associates, that degeneration of cartilage and osteophytes at the articular surfaces are present in over 80% of people past 40.

Clinical symptoms, however, develop in not more than 5 to 10%. Indeed, spurs are seen in most roentgenograms of people over middle age, who have never experienced trouble in their joints. Figures 1 and 2 show that Roentgen rays may give erroneous impressions even of bone lesions. Figure 1 was diagnosed by the roentgenologist of a large orthopedic hospital as an ankylosis of the patella.

In Figure 2 the patella was reported to be separated from the femur. Clinical examination, however, revealed the contrary to be true. After having satisfied himself that the patella in Figure 1 was, to his great surprise, freely moveable and in Figure 2 bound down evidently by adhesions, this roentgenologist discontinued to make a definite diagnosis and confined himself to describing impressions conveyed by the Roentgen ray pictures. The reservation of the final decision to the clinician is of benefit to both. It will be a great stimulus to develop advanced methods for registering the soft tissues.

A beginning was made in this direction by the inflation of air or other gases or by the injection of contrast media, like abrodil, into the joint cavity. These methods, under favorable circumstances, show changes in the soft tissues, like tears in the cartilages or hypertrophy of the synovial membrane. Unlike bone changes, soft tissue lesions are almost invariably associated with clinical symptoms. The greatest effort is indicated to advance our knowledge of their structure and behavior in health and disease.

The Synovial Tissue and the Normal Synovial Fluid. Until recently the synovial lining was commonly regarded to be a modified connective tissue devoid of specific function. Accordingly, normal synovial fluid was held to be a transudate with which soft tissue debris was admixed. The great variety in the number, size and shape of the synovial-lining cells and of the subsynovial tissue in

different sections of the joint was explained by the action of external factors like stress and pressure (Key⁴).

In 1919, however, Mayeda⁷ demonstrated, chiefly in the knee joint of rabbits, special cells in well defined areas which contained Heidenhain and Altmann granules, regarded as indicating a secretion mechanism. Other cells gave a positive oxidase reaction and absorbed colloidal dyes and particles like India ink, iron and silver injected either intraarticularly or intravenously. In these areas, therefore, evidence of absorption and secretion was present.

Fisher¹ also found mucin in cells of synovial villi stained with thionin. My attempts to duplicate these findings with thionin were not successful. By modified toluidin blue staining of sections and scrapings of normal human knee joints, I found, chiefly in the synovial lining of the fat pads and the villi and fornix of the suprapatellar pouch, cells containing reddish-purple metachromatic granules (Kling^{5h}). According to Metzner, these granules represent mucin or the precursor of mucin. Vaubel⁹ confirmed the presence of these granules in cells of tissue cultures of synovial membrane of rabbits. He found the same variety of cells in the culture explantes as have been found *in vivo*. These variations are, therefore, not dependent on extraneous factors, but present a biological property of synovial tissue.

These morphologic and experimental studies have restored the synovial lining from the rôle of a passive connective tissue capsule, to that of an active organ, equipped with specific functions. The most important of these is the elaboration of mucin.

The Synovial Mucin. The presence of mucin in synovial fluids is demonstrated by a simple precipitation test: a drop of synovial fluid is let fall into a test tube with 2% acetic acid. A membrane is formed, which envelops the contents like a sac or tube (Fig. 5). Blood plasma, transudates and exudates give only various degrees of turbidity in the acetic acid.

On the basis of extensive studies (Kling^{5a-g,m,6a,b} the following conclusions were drawn:

1. Mucin was found in each of 25 normal synovial fluids and in 94% of 200 synovial effusions of inflammatory or traumatic origin.

2. Mucin is responsible for the high viscosity of normal synovial fluid (from 10 to 20 times that of water) and for the wide fluctuation in the viscosity of effusions (from 1.6 to 102 times the viscosity of water, determined by the Hess viscosimeter). After precipitation of mucin, the viscosity of the supernatant fraction of synovial fluid drops to between 0.9 and 1.8.

3. Human synovial mucin is not a degeneration product from cartilage, because it does not markedly reduce copper sulphate, even after prolonged hydrolysis with hydrochloric acid, while chondromucin does so readily. It is not a tissue débris, because it does not redissolve in an excess of acetic acid and does not contain phosphorus-like nucleoprotein.



FIG. 1

FIG. 1.—Roentgen ray diagnosis—ankylosis of the patella. Clinically, patella freely movable.

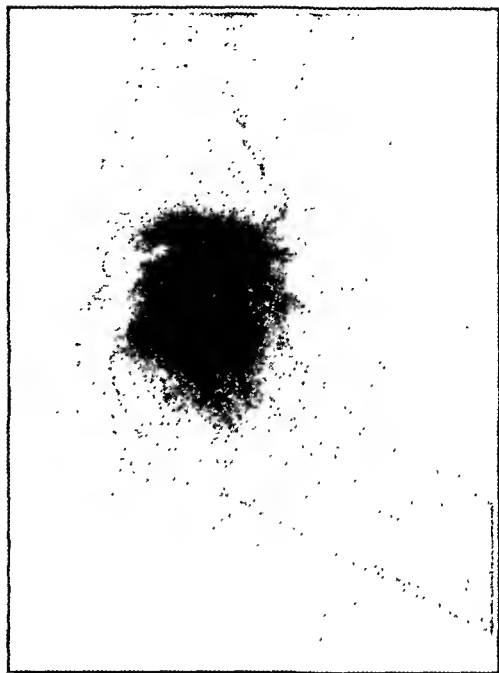


FIG. 2

FIG. 2.—Roentgen ray diagnosis—patella free. Clinically, patella bound by adhesions.



FIG. 3.—Villus from normal synovial lining of human knee joint. Modified toluidine blue stain. Arrow points to 3 large cells filled with metachromatic purple and red granules (mucin).

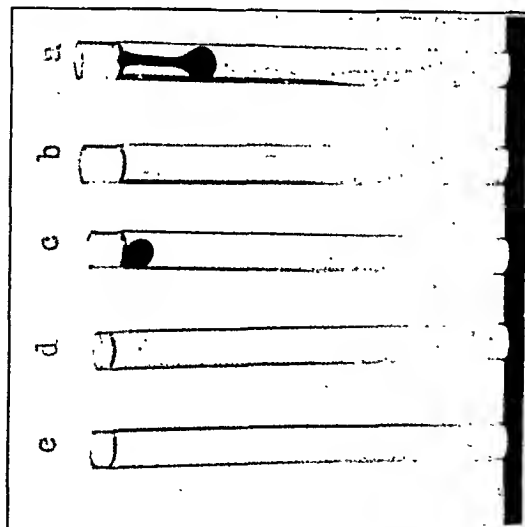


FIG. 4

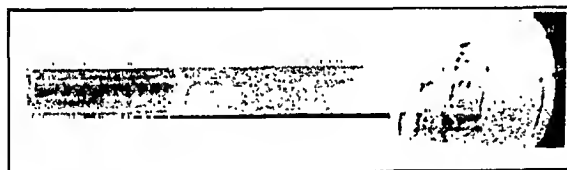


FIG. 5

FIG. 6

FIG. 4.—Precipitation phenomenon of a drop of synovial fluid in 2% acetic acid. *A* and *C* show sac and tube formation. *D* shows a thin sac. *B* is a drop of pleural fluid, showing slight turbidity and no sac. *E* is a drop of transudate; the fluid remains entirely clear.

FIG. 5.—Illustrates acid binding power of synovial mucin. Addition of 10% hydrochloric acid resulted in tube formation which envelops the acid.

FIG. 6.—Advanced case of juxtaarticular adiposa dolorosa. Notice the bulging fat pads at inner sides of knees which were hypersensitive to touch. Roentgen ray of knee joint was negative.

4. It is a physiologic product of specific activity as evidenced by morphologic studies and *in vitro*. Vaubel⁹ found that the minute amounts of fluid in synovial tissue cultures gave positive sac and tube precipitation, as long as the cultures remained healthy. As soon as degeneration had set in, this test for mucin was negative.

5. Mucin is the chief component of normal synovial fluid and the one on which its physiologic action depends.

The Functions of Synovial Fluid. The main function of synovial fluid is the protection of articular surfaces by: 1, proper lubrication, secured by high viscosity, and 2, acid-binding power of the synovial mucin.

Cartilage is seriously damaged, even by short action of acids. It is exposed to the detrimental action of acid metabolites, which accumulate during inflammation. The acid-binding power of the synovial mucin is demonstrated by a simple experiment:

A small test tube is partly filled with synovial fluid; a drop of methyl orange is added. Most synovial fluids, being alkaline, take a yellow tint with this indicator. Several drops of 10% hydrochloric acid are let fall into the tube. The hydrochloric acid sinks, enveloped in a membrane-like covering which forms a tube and sac. While the rest of the fluid remains yellow, the contents of the tube and the sac change to red, which proves that they contain the hydrochloric acid (Fig. 6). The binding of the acid is permanent. The contents, even after prolonged standing do not take the uniform red color observed in the plasma, transudates or exudates. The chemical properties of the mucin are therefore a factor in the maintenance of the high degree of alkalinity observed even in inflammatory effusions and in the protection of articular cartilage from the acid metabolites.

3. A number of ferments were found in normal synovial fluids of cattle by Podkaminsky⁸ such as amylase, lipase and a protease. The proteolytic ferment is of special interest because it was observed also in tissue cultures, causing liquefaction of the media, proving it to be a product of the synovial tissue and not imported by the circulation. The presence of digestive ferments points to another protective property of synovial fluid, namely the digestion of the inflammatory or traumatic products, which precipitate within the joint cavity, such as fibrin, tissue débris, or fat particles.

The Bio-mechanical Significance of Joint Lubrication. Recently Jones² has experimentally proved on the stifle joints of horses the great importance of proper lubrication. The coefficient of friction amounted in dry joints to 14 times as much as in joints kept lubricated. In the latter, after 4 hours of mechanical motion, the joint surfaces were undamaged. In the dry joints, the internal semilunar cartilage and the condyle of the femur were worn down. The joint was steaming hot and grating was felt. Motion without lubrication has therefore produced changes encountered in some forms of chronic arthritis.

The rich supply of vessels and capillaries in the synovial membrane serves not only to secure the exchange of fluids between circulation and joint cavity, but also to remove the heat produced by the motion.

The Reaction of Synovial Tissue to Injury and Inflammation and the Composition of Joint Effusions. Both trauma and inflammation induce pathologic changes, the degree of which depends on their severity, extent and duration. The wall is damaged in the first case mechanically; in the second by exudation and infiltration; the capsule is distended by hemorrhage or exudate from the circulation. Noxious metabolites are present both in the disintegrating hematrosis and in the inflammatory exudate. Both contain fibrin and other particles, which irritate the joint tissues. The response of the synovial tissue is, therefore, alike in both injury and trauma, namely, hyperfunction of the intact parts resulting in an increased output of synovial fluid. A prolonged duration of the irritation results in hypertrophy of the synovial membrane (villous synovitis).

Both traumatic and inflammatory effusions, therefore contain: 1, elements from the synovial lining (mucin, ferments, and synovial lining cells); 2, elements from the circulation (blood cells, plasma, enzymes, antibodies or fibrin).

The quantitative and qualitative relation of these elements determines the character of the pathologic joint effusion. In acute virulent inflammation the exudate prevails. The quantity is large, the turbidity marked, and the viscosity is low. The cell count is high and polynuclear leukocytes prevail. In chronic synovitis, the synovial elements predominate. The fluid is viscid, clear or contains suspended particles. The number of the synovial lining cells is increased.

Certain forms of arthritis have special features, such as high fibrin and globulin content in gonorrheal arthritis, abundance of debris in tuberculous arthritis and suspended particles in osteoarthritis.

The Clinical Value of Aspiration of Joint Effusions. A widespread prejudice against aspiration of joint effusion has retarded knowledge of joint lesions, has deprived the clinician of an excellent diagnostic aid and the patient of a beneficial therapeutic measure. In several thousand aspirations of traumatic and inflammatory (including tuberculous) joint effusions, I have not seen a single instance of an untoward effect. The therapeutic effect of evacuation of traumatic effusions is self-evident. Even in inflammatory effusion the temporary relief of distention and the removal of the toxic products are of decided benefit. I have frequently found on reaspiration the reaccumulated effusion to contain fewer cells or to have a lower viscosity than the original fluid. The therapeutic result of repeated aspiration was especially striking on gonorrheal arthritis.

Table 1 gives a review of a method of systematic examination of synovial effusions and the diagnostic significance of the tests.

TABLE 1.—SYSTEMATIC EXAMINATION OF JOINT EFFUSIONS.

Tests.	Significance.
1. Quantity	Large—in active and severe inflammation. Small—in mild, chronic arthritis.
2. Turbidity	(a) Homogeneous—depends on number of cells; (b) non-homogeneous—depends on suspended particles, such as fibrin or débris.
3. Reaction (pH or litmus)	Acid reaction in septic arthritis. Alkaline reaction on repeated aspiration indicates favorable prognosis.
4. Viscosity (Hess viscosimeter)	High viscosity in chronic arthritis. Low viscosity in acute inflammation or transudate.
5. Precipitation (2% acetic acid)	Sac and tube indicate mucin.
6. Fat in traumatic effusions (centrifuge)	Severe injuries to fat pads, menisci or intra-articular fracture.
7. Bilirubin	High icteric index (over 5) in traumatic. Low (under 5) in most inflammatory effusions.
8. Culture	(a) Septic arthritis: ready growth in routine cultures (streptococci, staphylococci, pneumococci, etc.); (b) acute gonorrheal arthritis: positive 10 to 25%; (c) tuberculous arthritis: cultures supplement the guinea-pig inoculation; often positive within 14 days; (d) chronic, atrophic and hypertrophic arthritis: routine cultures negative. Special method after prolonged incubation in 10 to 20% positive, chiefly for streptococci, staphylococci and diphtheroids. Etiological significance doubtful.
9. Animal inoculation	Standard method for tuberculosis.
10. Stained smears	Positive in septic arthritis, advanced tuberculosis and occasionally in acute gonorrhea.
11. Sections of suspended particles	For microscopic study of their nature and histologic structure.
12. Cell count	High (above 10,000 per c.mm.) in acute, severe stages, regardless of etiology. Low in mild, chronic and inactive conditions.
13. Differential count	(a) Predominance of neutrophils in acute stages, regardless of etiology; (b) lymphocytes, monocytes in chronic stages; (c) increase in synovial cells (over 10%) indicates hypertrophy of synovial wall (villus synovitis).
14. Wassermann	Clarifies etiology.
15. Gonococcus complement-fixation test	Positive in subacute and chronic gonorrheal arthritis.
16. Comparative sedimentation (blood and synovial fluid)	Indicates the condition of an affected joint and its rôle in polyarthritis.
17. Uric acid	Assists in differential diagnosis of gout.

The Periarticular Tissues. Careful examination often reveals that symptoms assumed to originate in the joints are due to changes in the periarticular structures, consisting of diffuse or localized contraction of the muscle, tenderness at the insertion of the tendons, and subcutaneous nodules. The inflammation of smaller joints is often combined with tenosynovitis.

*Juxtaarticular Adiposis Dolorosa.*⁵⁷ Hypersensitivity and enlargement of the subcutaneous fat, especially around the knee (Fig. 6) and elbow joints, are frequently present in obese women past middle

age who complain of pain and stiffness in the extremities. A report of 112 cases of this condition which I have termed Juxtaarticular Adiposis Dolorosa, presents evidence of its important rôle as an etiologic factor in the development of osteoarthritis. This condition is usually associated with other periarticular changes of the soft tissues and circulatory disturbances, hypertension, varicose veins and acroparesthesia. Evidences also of hypo- and dysfunction of the endocrine glands, especially ovaries, pituitary and thyroid, are found. The condition is usually overlooked in a superficial examination of the joints and the tenderness is erroneously assumed to originate in the articular structures, the more so, since in about 60% Roentgen rays show osteophytic changes in the articular surface. The latter are not more extensive, however, than should be expected in this age group.

From a therapeutic standpoint the diagnosis of periarticular changes is important. Stenosing tenosynovitis of the abductor longus and the extensor brævis tendons of the thumb is often diagnosed and futilely treated as arthritis of the wrist, while a simple operative procedure which frees the tendon from the stricture produces an instantaneous and permanent cure. The recent introduction of histamine by cataphoresis has proved to be of beneficial effect in the pathologic conditions of the periarticular structures (Kling ⁵³⁻⁴).

Summary. 1. Less speculation and more facts on joint pathology and physiology are needed for progress in research and therapy of arthritis and rheumatic conditions.

2. Bone changes as seen in routine roentgenograms are over-emphasized and too little attention is given to the soft, intra- and extraarticular structures.

3. Morphologic, physiochemical studies and experiments show a dual structure and function of the synovial tissues; one part is a connective capsule for the binding of articulating bones. Interposed at the intraarticular surfaces are areas for the elaboration of the synovial fluid.

4. The function of normal synovial fluid is lubrication and protection of the joint surfaces.

5. Motion is the physiologic stimulus for the production of normal synovial fluid.

6. The function of normal synovial fluid depends on its content of mucin.

7. Mucin is a product of special cell activity and not of degeneration.

8. The biochemical importance of proper joint lubrication is stressed.

9. The therapeutic value of aspiration of traumatic and inflammatory effusions is pointed out.

10. The diagnostic significance of a systematic examination of joint effusions is reviewed.

11. Changes in the periarticular structures such as infiltration of the insertion of tendons, subcutaneous tissues and atrophy of muscles and tenosynovitis are frequently present and play an important rôle in the pathology of arthritis.

12. Hypersensitivity of the subcutaneous fat, especially at the knee and elbow joints (*juxtaarticular adiposis dolorosa*), is a frequent etiologic factor in the development of osteoarthritis in obese women past middle age.

13. In the therapy of soft tissue changes in arthritis, histamine cataphoresis has proven to be of value.

REFERENCES.

- (1.) Fisher, A. G. T.: *Lancet*, 2, 54, 1923. (2.) Jones, E.: *Ibid.*, 1, 1425, 1934. (3.) Keefer, C. S., Parker, F., Jr., Myers, W. K., and Irwin, R. L.: *Arch. Int. Med.*, 53, 325, 1934. (4.) Key, A.: *Synovial Membrane in Special Cytology*, New York, Paul B. Hoeber, Inc., vol. 2, 1928. (5.) Kling, D. H.: (a) *Am. J. Surg.*, 6, 71, 1929; (b) *Am. J. Syph.*, 13, 596, 1929; (c) *Arch. Surg.*, 20, 17, 1930; (d) *J. Bone and Joint Surg.*, 12, 867, 1930; (e) *Ann. Surg.*, 94, 389, 1931; (f) *Arch. Int. Med.*, 50, 419, 1931; (g) *Deutsch. Arch. f. klin. Med.*, 172, 165, 1931; (h) *Arch. Surg.*, 23, 543, 1931; (i) *Am. J. Med. Sci.*, 183, 538, 1932; (j) *Ann. Surg.*, 99, 568, 1934; (k) *Arch. Surg.*, 29, 138, 1934; (l) *Arch. Phys. Therap.*, 16, 466, 1935; (m) *Arch. Surg.*, 30, 52, 1935; (n) *Ibid.*, 34, 599, 1937. (6.) Kling, D. H., and Pincus, J.: (a) *Am. J. Syph.*, 15, 367, 1931; (b) *J. Lab. and Clin. Med.*, 17, 39, 1931. (7.) Mayeda, T.: *Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo*, 23, 393, 1919-1920. (8.) Podkaminsky, N. A.: *Compt. rend. Soc. de biol.*, 105, 915, 1931. (9.) Vaubel, E.: *J. Exp. Med.*, 58, 63, 1933.

THE FORMOL-GEL REACTION.

A CONVENIENT PRELIMINARY TEST FOR HYPERGLOBULINEMIA.

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SERA of most patients with kala-azar rapidly form a solid, opaque white gel upon the addition of one or two drops of formalin.^{12a,14} This phenomenon, commonly known as the formol-gel test, and used extensively for the diagnosis of kala-azar, depends upon the presence in the serum of increased amounts of globulin.^{12b} A positive formol-gel reaction is obtained also in other diseases in which marked hyperglobulinemia may develop, notably in cases of multiple myeloma,^{2,6,15} lymphogranuloma inguinale^{16,6} and hepatic

cirrhosis⁶; and in occasional cases of malaria, leprosy, tuberculosis, subacute bacterial endocarditis, etc.^{10,17}

In the present study, the usefulness of the formol-gel reaction has been investigated, not as a diagnostic test, but as a means for detecting hyperglobulinemia irrespective of etiology. Since its adequacy for this purpose would depend upon the consistency with which positive reactions are obtained with hyperglobulinemia, and negative reactions with normal serum globulin levels, we record here the results of the formol-gel test in 113 sera of which the content of total protein and of the several protein fractions was determined. Our data suggest that this simple reaction is consistent enough to serve as a convenient preliminary test for the detection of hyperglobulinemia of diverse origin.

It should be made clear, however, that prompt opaque-gel formation does not occur in the presence of only moderate hyperglobulinemia. In order to detect increases in serum globulin content of lesser magnitude than may occur in kala-azar, it was found necessary to make observations at the end of 24 hours and to regard as positive less striking changes in gelation and opacity than are obtained in kala-azar. This proved feasible since, with rare exceptions, sera with globulin contents within normal limits (obtained from normal subjects and from patients with a wide variety of diseases) showed no change 24 hours after addition of formol. A clinically practical schema for the quantitation of the formol-gel reaction is presented.

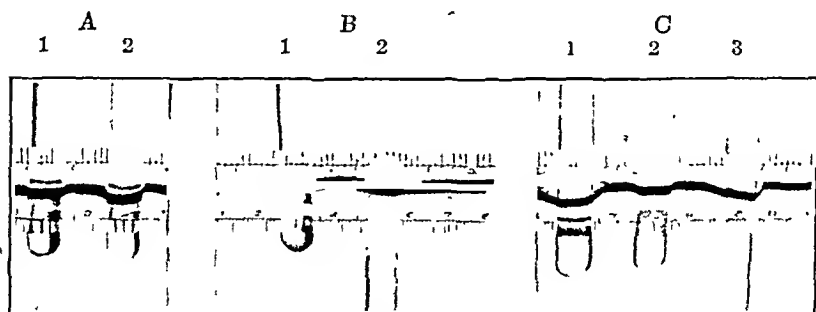


FIG. 1.—Illustrative formol-gel reactions. A, Normal serum (tot. prot., 6.3; alb., 4.6; glob., 1.8). No change in opacity or gelation after 24 hours. B, Case 27 (hepatic cirrhosis; tot. prot., 7.9; alb., 2.1; glob., 5.8). 4+ opacity and gelation after 5 minutes. C, Case 30 (hepatic cirrhosis; tot. prot., 7.2; alb., 2.4; glob., 4.8). No change after 5 minutes. 2+ opacity change and 3+ change in gelation after 2 hours. 3+ opacity and 4+ gelation after 24 hours.

Method. The formol-gel test is performed as follows: 1 cc. serum obtained from fasting patients is placed in a small test tube (8 mm. bore is a convenient size), 2 drops of approximately 40% formaldehyde solution are added, the whole is mixed and stoppered, and allowed to stand at room temperature. Since gelation and opacity may be due to different factors^{3,6,8a} changes in both were recorded separately. Ordinarily, however,

the two phenomena occur together in positive sera, though in occasional cases only one or the other develops. Observations were made at arbitrarily selected periods of 5 minutes, 2 hours and 24 hours (Table 1, Fig. 1). This procedure proved better than attempting to record the results as the time which elapsed before specified alterations in opacity or gelation developed.

TABLE 1.—FORMOL-GEL REACTION IN 7 CASES OF MULTIPLE MYELOMA (M.M.), 16 CASES OF LYMPHOGRANULOMA INGUINALE (L.I.), 11 CASES OF CIRRHOSIS OF THE LIVER (C.L.), AND 12 MISCELLANEOUS CASES.

Case.	Diagnosis.	Serum proteins.				Formol-gel reaction of serum.					
		Total prot., %.	Albumin, %.	Globulin, %.	Euglobulin, %.	Gelation.			Opacity.		
						1/12	2 hours.	24	1/12	2 hours.	24
1	M.M.	11.1	2.3	8.8	0.4	4+	4+	4+	4+	4+	4+
2	M.M.	8.9	2.5	6.4	4.4	4+	4+	4+	4+	4+	4+
3	M.M.	9.2	3.1	6.1	2.3	4+	4+	4+	4+	4+	4+
4	M.M.	8.6	3.8	4.8	1.8	—	—	3+	—	1+	3+
5	M.M.	6.6	2.7	3.9	0.3	—	—	2+	—	—	—
6	M.M.	6.3	3.1	3.2	0.6	—	—	—	—	—	—
7	M.M.	7.7	5.4	2.3	0.4	—	—	—	—	—	—
8	L.I.	11.1	3.3	7.8	3.2	4+	4+	4+	1+	2+	2+
9	L.I.	9.7	3.5	6.2	2.4	2+	4+	4+	2+	3+	3+
10	L.I.	9.9	3.8	6.1	2.3	3+	4+	4+	1+	2+	2+
11	L.I.	9.5	3.4	6.1	2.3	—	4+	4+	—	3+	4+
12	L.I.	9.1	3.1	6.0	2.4	2+	4+	4+	2+	2+	2+
13	L.I.	9.6	3.7	5.9	2.3	2+	4+	4+	1+	1+	1+
14	L.I.	9.1	3.5	5.6	2.9	—	4+	4+	—	4+	4+
15	L.I.	9.0	3.5	5.5	2.3	—	3+	4+	1+	2+	3+
16	L.I.	8.7	3.4	5.3	1.7	—	4+	4+	—	3+	4+
17	L.I.	8.6	3.6	5.0	1.7	—	4+	4+	—	2+	2+
18	L.I.	8.5	3.7	4.8	0.9	—	3+	4+	—	2+	4+
19	L.I.	8.1	3.3	4.8	1.5	—	1+	2+	—	—	2+
20	L.I.	8.6	3.9	4.7	1.7	—	2+	4+	—	—	2+
21	L.I.	8.0	3.5	4.5	1.5	—	4+	4+	1+	2+	2+
22	L.I.	7.5	4.1	3.4	0.9	—	—	—	—	—	—
23	L.I.	7.0	3.7	3.3	1.1	—	—	2+	—	—	1+
24	C.L.	9.5	2.2	7.3	0.5	—	4+	4+	1+	4+	4+
25	C.L.	8.4	2.4	6.0	2.1	1+	4+	4+	1+	4+	4+
26	C.L.	9.6	3.7	5.9	2.8	2+	4+	4+	—	1+	2+
27	C.L.	7.9	2.1	5.8	3.3	4+	4+	4+	4+	4+	4+
28	C.L.	7.4	1.8	5.6	2.2	—	4+	4+	1+	2+	3+
29	C.L.	7.2	2.2	5.0	1.7	—	3+	4+	—	2+	4+
30	C.L.	7.2	2.4	4.8	1.6	—	3+	4+	—	2+	3+
31	C.L.	7.4	2.8	4.6	1.3	—	—	4+	—	—	1+
32	C.L. (Banti's)	8.1	4.4	3.7	1.2	—	—	4+	—	—	4+
33	C.L. (Banti's)	6.6	3.3	3.3	0.7	—	—	—	—	—	—
34	C.L.	8.1	5.4	2.7	0.4	—	—	—	—	—	—
35	Syphilis	9.7	4.0	5.7	1.9	—	3+	3+	—	1+	2+
36	Undiagnosed	9.1	4.3	4.8	—	1+	3+	4+	2+	2+	2+
37	Undiagnosed	7.5	3.0	4.5	1.3	—	1+	3+	—	—	2+
38	Rheum. arthritis	9.0	4.6	4.4	1.1	—	—	4+	—	—	1+
39	Sarcoid (Boeck)	8.5	4.0	4.5	1.5	—	1+	3+	—	—	—
40	Hyper. cardiae	7.6	3.7	3.9	0.9	—	—	3+	—	—	—
41	Empyema	6.2	2.4	3.8	1.3	—	2+	3+	—	1+	2+
42	Ca., bone met.	7.6	4.0	3.6	—	—	—	—	—	—	—
43	Hepatitis	8.0	4.4	3.6	0.6	—	—	3+	—	—	—
44	Myxedema	7.0	3.6	3.4	0.9	—	—	3+	—	2+	2+
45	Hepatitis	6.9	4.1	2.8	0.5	—	—	—	—	—	—
46	Nephrosis	3.8	1.2	2.6	—	—	—	—	—	—	—

Changes in viscosity were recorded as follows: — or =, no or questionable increase in viscosity; +, increased viscosity, definitely oily flow on tilting the tube; 2+, very viscous, a thick, slow-moving fluid; 3+, semi-solid, no flow on inversion but jelly-like quiver on tapping the tube; 4+, solid. Care should be taken in reading 24-hour changes to break up the surface film which frequently forms. Changes in opacity were recorded as

follows: — or \pm , no or questionable opalescence or haziness; +, opalescent, a faint haziness; 2+, translucent, milky, but freely transmitting light; 3+, semiopaque, cloudy but transmitting light; 4+, opaque. More accurate measurements of changes in viscosity and opacity by means of a viscometer and photometer seemed unnecessary for our purpose.

Except when associated with hyperglobulinemia, the presence of jaundice, anemia, lipemia; hypercholesterolemia, nitrogenous retention products or hemolysis does not result in positive reactions.* When lipemia is present, opacity changes are difficult to read, hence fasting samples should be used. If the original serum is not clear, a sample should be used as a control standard for comparison with formol-tested specimens. The temperature of the reaction, between 0 and 38° C., does not affect the results appreciably. The effects of prolonged tourniquet stasis and of dehydration were not studied.

Plasma should not be used, as we frequently obtained positive reactions with plasma in a variety of diseases when the corresponding serum was negative. It would appear that the presence of even moderately increased fibrinogen will cause the formol-gel reaction to become positive.

Total protein of the serum was determined by difference on 1 cc. samples, the micro-Kjeldahl technique being used for total nitrogen and Folin's method with Nesslerization for non-protein nitrogen. Serum protein partitions were carried out in duplicate on 0.5 cc. samples by Howe's method.

RESULTS. The results of the formol-gel test in 113 cases were tabulated as shown in Table 1, which includes representative observations in 46 cases, with associated serum protein values. It is apparent from Table 1 that a general correlation exists between positive formol-gel reactions and the level of total protein and globulin in the serum. An analysis of this correlation in our entire series of 113 observations is presented in Tables 2 and 3. It should be emphasized that for the purpose of this analysis a positive reaction is defined as a change in viscosity or opacity of 1+ or more after 24 hours.

1. *Relation of positive formol-gel test after 24 hours to total protein and globulin content of the serum.* As indicated in Table 2, 23 of 24 cases with total proteins of 8.5% or more showed definitely increased viscosity, and 22 of 24 developed changes in opacity in 24 hours. All sera with globulin contents of 4% or more showed an increase in viscosity; all but one developed some degree of opacity. These results suggest that marked hyperproteinemia and hyperglobulinemia can be detected satisfactorily by the formol-gel test.

Conversely, in sera with globulin levels below 3.4%, *i. e.*, in sera without hyperglobulinemia, the formol-gel test was consistently negative, only one slightly positive result being obtained in this group (3.3%, Case 23, Table 1). Positive reactions may be ob-

* This conclusion is supported by negative formol-gel tests obtained on more than 100 sera of patients with catarrhal jaundice, syphilis, anemias, nephritis, diabetes, neoplasms, infections and a variety of other diseases. These miscellaneous cases, which serve as an additional control group, are not included in our statistical analysis because serum proteins were not determined. Hyperglobulinemia, with positive formol-gel reactions, occasionally occurs in these diseases, however (Table 1).

tained, however, when the *total* serum protein is below the accepted upper limit of the normal range, 8%, if hyperglobulinemia is present (Table 3). Such sera are comparable to those with total protein levels above 8% in that they contain 3.4% or more globulin, but the total protein content is not increased because of a concomitant decrease in albumin.

TABLE 2.—A. CORRELATION BETWEEN PERCENTAGE OF TOTAL SERUM PROTEIN AND FORMOL-GEL REACTION. B. CORRELATION BETWEEN PERCENTAGE OF SERUM GLOBULIN AND FORMOL-GEL REACTION.

A. Total Serum Protein.									
Total protein, %.		42 cases. <7.0.		36 cases. 7.0 to 8.0.		11 cases. 8.0 to 8.5.		24 cases. > 8.5 or more.	
		Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
5 min.	Opacity . . .	0	42	2	34	4	7	12	12
	Gelation . . .	0	42	1	35	3	8	11	13
2 hrs.	Opacity . . .	1	41	6	30	5	6	20	4
	Gelation . . .	1	41	4	32	6	5	20	4
24 hrs.	Opacity . . .	2	40	9	27	7	4	22	2
	Gelation . . .	2	40	12	24	10	1	23	1

B. Serum Globulin.									
Globulin, %.		52 cases. <3.4.		26 cases. 3.4 to 4.0.		35 cases. > 4.0 or more.			
		Pos.	Neg.	Pos.	Neg.	Pos.	Neg.		
5 min.	Opacity . . .	0	52	0	26	18	17		
	Gelation . . .	0	52	0	26	15	20		
2 hrs.	Opacity . . .	0	52	3	23	29	6		
	Gelation . . .	0	52	1	25	30	5		
24 hrs.	Opacity . . .	1	51	5	21	34	1		
	Gelation . . .	1	51	11	15	35	0		

TABLE 3.—THE FORMOL-GEL TEST IN 113 SERA, TO SHOW THE INCIDENCE OF POSITIVE RESULTS WITH ELEVATED SERUM GLOBULIN, IRRESPECTIVE OF TOTAL SERUM PROTEIN LEVEL.

	Serum globulin, %	No. of cases.	Formol-gel reaction.	
			Pos.	Neg.
Total serum protein below 7%	<3.4	34	0	34
	3.4-4	8	3	5
	>4.0	0	0	0
Total serum protein, 7 to 8%	<3.4	17	1	16
	3.4-4	13	4	9
	>4.0	6	6	0
Total serum protein above 8%	<3.4	1	0	1
	3.4-4	5	4	1
	>4.0	29	29	0

Sera containing 3.4 to 4% globulin form an intermediate group, the recognition of which by means of the formol-gel test is uncertain. Only 11 of 26 cases in this group gave a positive reaction in 24 hours.

2. *Relation of (a) rapidity and (b) intensity of the formol-gel reaction to the globulin content of the serum.* As recorded in Table 2, positive reactions developing within 5 minutes or 2 hours occur, with few exceptions, only in sera with marked hyperproteinemia. Similarly, of 35 sera with globulin contents of 4% or over, 18 were positive in 5 minutes and 30 became positive in 2 hours. Only 5 such sera required more than 2 hours to develop positive reactions. Most

positive reactions obtained in sera with globulin contents between 3.4 and 4%, on the other hand, required more than 2 hours to develop. It would seem, therefore, that sera with globulin contents in the higher ranges develop the formol-gel reaction more rapidly; consequently, if positive reactions develop within 5 minutes, globulin contents exceeding 4% may be inferred.

Thus far we have considered the outcome of the formol-gel test only in terms of positive results, without making any distinction between 1+, 2+, 3+ or 4+ changes in gelation or opacity. If the results are analyzed as regards intensity of the reaction it becomes apparent that 3+ and 4+ reactions were obtained within 5 minutes only in sera containing well over 5% globulin. And as regards opacity changes, 3+ or 4+ reactions even at the end of 24 hours were obtained only in sera with globulins of 4.8% or over.

It is interesting to note that while practically all sera containing 4% or more of globulin developed opacity changes, some with very high globulin content did not give 3+ or 4+ reactions even at the end of 24 hours. There is, in fact, a considerable variation in the intensity of the opacity reaction obtained in sera containing approximately the same amount of globulin. These variations are so marked as to suggest that the quantity of globulin present is not the only factor responsible for opacity changes, but that qualitative differences in the several globulin fractions also play a rôle. There is experimental evidence in support of this view.^{3,6,8a}

Discussion. It is apparent that the formol-gel reaction is a diagnostic aid only insofar as it is positive in diseases presenting hyperglobulinemia. Rapid formation of a solid opaque or semi-opaque gel does indicate the presence of such high globulin levels as are found chiefly in multiple myeloma, kala-azar, hepatic cirrhosis, lymphogranuloma inguinale and leprosy; and occasionally in other diseases.^{1,4,8b,9,11,13} But moderate elevations in serum globulin, with 1+ or 2+ changes in gelation or opacity at the end of 24 hours are encountered in a variety of diseases, chiefly infectious, and are of little value in diagnosis.

The formol-gel reaction as a means of detecting hyperglobulinemia would seem to be useful in studies on the variation of serum proteins in disease. It may serve as a convenient preliminary method for selecting sera for protein fractionation, obviating the necessity for laborious analyses on negative sera. The test makes feasible the examination, on a more comprehensive scale than is ordinarily possible, of sera from patients with unexplained high sedimentation rates, hepatic disease, unexplained anemia, tuberculosis, etc. It should be emphasized, however, that the formol-gel test gives only an approximation of the degree of elevation in serum globulin content, and is obviously no substitute for serum protein fractionation unless facilities for the latter are unavailable.

Our data are in accord with the view that opaque-gel formation

depends upon the presence of an increase in the serum globulin fraction, irrespective of whether or not the total protein content is elevated. Since hyperglobulinemia is ordinarily the result chiefly of increases in the euglobulin fraction, as determined by Howe's method, the formol-gel reaction has been ascribed solely to hyper-euglobulinemia. Strongly positive results are obtained, however, in occasional sera with hyperglobulinemia due only to an increase in the pseudoglobulin fraction (Cases 1, 24, Table 1). We conclude, therefore, that opaque-gel formation is dependent upon the presence of "abnormal" globulins,* irrespective of whether their solubility characteristics with regard to sodium sulphate correspond with those of euglobulin or pseudoglobulin.

Concerning the chemical mechanism of the formol-gel test, nothing is known. The added formaldehyde presumably combines with the free NH_2 groups of the protein molecules.^{5,7} But the precise nature of the changes in structure or in state of hydration that take place is, as yet, wholly obscure.

Summary. 1. The formol-gel test was performed in 113 sera of which the content of total protein and of the several protein fractions was determined. The results of the formol-gel reaction were quantitated according to a clinically practical schema in which changes in gelation and opacity were recorded at arbitrarily selected periods of 5 minutes, 2 hours and 24 hours. The rapidity and intensity of changes in gelation and opacity were correlated with the content of total protein, globulin and the several globulin fractions.

2. All but one of 24 sera with total proteins of 8.5% or more and all but one of 35 with globulin of 4% or more showed changes in viscosity and opacity within 24 hours. Conversely, all but one of 52 sera with globulin levels below 3.4% were negative after 24 hours. Sera containing 3.4 to 4% globulin could not be detected consistently by means of the formol-gel test. Sera with total proteins less than 8% gave positive results if hyperglobulinemia was present.

3. Of 35 sera with globulin contents of 4% or over, 30 became positive within 2 hours. Most positive reactions obtained in sera with globulin contents between 3.4% and 4%, on the other hand, required more than 2 hours to develop. Formation of an opaque or semiopaque-gel within 5 minutes occurred only in sera containing well over 5% globulin.

4. Our data suggest that the formol-gel reaction is consistent enough to serve as a convenient preliminary test for the detection

* "Abnormal" is used here to imply altered globulins apparently not present in normal serum. Reference has already been made to empirical and experimental evidence for qualitative differences in globulins, and to the probable causal relation of such differences to opacity changes. It is interesting to note in this connection that the minimal serum globulin level at which positive formol-gel reactions (as here defined) begin to appear corresponds closely with the accepted maximal level of serum globulins in normal persons.

of hyperglobulinemia of diverse origin. Possible applications of the test are considered. The formol-gel reaction is a diagnostic aid only insofar as it is positive in diseases presenting hyperglobulinemia.

5. Our results are in accord with the view that the formation of an opaque gel is due to qualitative as well as quantitative changes in the serum globulin fraction. The altered serum globulins responsible for opaque gel formation do not have solubility characteristics with respect to sodium sulphate which permit of their classification as euglobulin or pseudoglobulin, as determined by Howe's method.

Addendum.—While this article was in press, our attention was called to a publication by S. Hetényi (*Verh. deut. Ges. inn. Med.*, 39, 342, 1927) in which the formol-gel reaction was proposed as a test for hyperglobulinemia. No data are given. Very recently an excellent study by J. Bing (*Acta Med. Scand.*, 91, 336, 1937) has appeared, describing the formol-gel reaction as a general test for hyperglobulinemia. The conclusions of Hetényi, Gutman and Wise,⁶ and Bing, are in general accord with ours as to the usefulness of the formol-gel reaction as a preliminary test for hyperglobulinemia, irrespective of etiology. For reasons stated in the text, we prefer to record the degree of opacity and gelation rather than that of gelation alone, as in the studies of Hetényi and Bing.

REFERENCES.

- (1.) Aldred-Brown, G. R. P., and Munro, J. M. H.: *Quart. J. Med.*, 4, 269, 1935.
- (2.) Bing, J.: *Acta med. Scand.*, 88, 478, 1936. (3.) Chopra, R. N., and Chaudhury, S. G.: *Indian J. Med. Res.*, 16, 925, 1929. (4.) Chopra, R. N., Mukherjee, S. N. and Rao, S. S.: *Ibid.*, 22, 171, 1934. (5.) Dulière, W. L.: *Biochem. J.*, 30, 770, 1936.
- (6.) Gutman, A. B., and Wise, C. R.: *Proc. Soc. Exp. Biol. and Med.*, 35, 124, 1936.
- (7.) Kekwick, R. A., and Cannan, R. K.: *Biochem. J.*, 30, 235, 1936. (8.) Lloyd, R. B., and Paul, S. N.: (a) *Indian J. Med. Res.*, 16, 203, 1928; (b) 17, 583, 1929.
- (9.) Lüthy, F.: *Schweiz. med. Wchnschr.*, 57, 993, 1927. (10.) Manson-Bahr, P. H.: *Manson's Tropical Diseases*, 10th ed., London, Cassel & Co., p. 157, 1935. (11.) Meleney, H. E., and Wu, H.: *China Med. J.*, 38, 357, 1924. (12.) Napier, L. E.: (a) *Indian Med. Gaz.*, 56, 338, 1921; (b) *Indian J. Med. Res.*, 9, 830, 1922. (13.) Salvesen, H.: *Acta med. Scand.*, 86, 127, 1935. (14.) Spackman, W. C.: *Brit. Med. J.*, 2, 266, 1921. (15.) Sweigert, C. F.: *Am. J. Med. Sci.*, 190, 245, 1935. (16.) Tasaki, K.: *J. Orient. Med.*, 24, 805, 1936. (17.) Troisier, J., and Bariety, M.: *Bull. et mém. Soc. d. hôp. do Paris*, 50, 522, 1934.

BOOK REVIEWS AND NOTICES.

MEDICAL GREEK AND LATIN AT A GLANCE. By WALTER R. AGARD, B. LITT. (OXON.), Professor of Greek, University of Wisconsin. With an Introduction by C. H. BUNTING, M.D., Professor of Pathology, University of Wisconsin. Pp. 87 (every other page blank). Second edition, revised. New York: Paul B. Hoeber, Inc., 1937. Price, \$1.50.

MANY medical terms sound so complicated to the lay ear that they have long been the subject of good-natured sarcasm in public utterances. Yet to the educated medical student such a word is not only usually self-explanatory; but, *multum in parvo*, conveys an extended meaning in a short space. With the unfortunate present day decline of the college man's "small Latin and less Greek" almost to the vanishing point, he is deprived of this royal road to medical terminology. This handbook has been prepared to lessen such damage. After a few pages of alphabet and pronunciation, it devotes 30 pages to words using frequently met prefixes and suffixes (such as "apathy," "ultrafiltration," "stenosis," "sarcoma") and compound words (including such bastards as "costochondral," "visceroptosis"). The next 30 pages list alphabetically important medical words with their derivation from Latin and Greek, and the book concludes with classified lists of colors, adjectives, substances, numbers, chemicals, parts of the body and so on. Inexpensively prepared, the book cannot be too warmly recommended for every medical student. In fact, if not otherwise available, its possession is urged as indispensable.

E. K.

READING, WRITING AND SPEECH PROBLEMS IN CHILDREN. A Presentation of Certain Types of Disorders in the Development of the Language Faculty. By SAMUEL TORREY ORTON, M.D., former Professor of Neurology and Neuropathology, Columbia University. Pp. 215; 24 illustrations. New York: W. W. Norton & Co., Inc., 1937. Price, \$2.00.

THIS study of disorders in the acquisition of the language faculty formed the basis of the author's recent Memorial Lecture. The meddlesome effort of some parents to overcome left-handedness in their children contributes to the development of certain speech disorders and merits condemnation. Among other problems discussed are troublesome forms of deafness, abnormal clumsiness and stuttering, all of which may hamper academic advancement or provoke emotional disorders.

As to matters of speech and manual dexterity: these are found to have a definitely restricted unilateral cerebral representation and it is shown that difficulties, the outcome of deviations in the process of establishing such unilateral brain superiority, may be prevented or removed by proper training.

There is no index, but since the work is not exclusively for physicians, the glossary supplementing the text will be found of infinite use to those parents and teachers who may become the fortunate possessors of this book.

N. Y.

SICKNESS AND INSURANCE. A Study of the Sickness Problem and Health Insurance. By HARRY ALVIN MILLIS, Professor of Economics, The University of Chicago. Pp. 166. Chicago: The University of Chicago Press, 1937. Price, \$2.00.

THE problem of economic security against sickness becomes more acute as progress is made in medical science and as the popular demand for the benefits of medical knowledge increases. How to meet the costs of adequate

medical care is now a serious problem before the American people, to which much thought is being given by the medical profession, and by economists and sociologists. This contribution by a professor of economics in a large university discusses the nature and dimensions of the problem of sickness, the various attacks that have been made upon it through social insurance and what health insurance in proper coördination with public health service may do in solving the problem of sickness in the United States.

The extent and costs of sickness are not easily defined, as it requires drawing a distinction between what actually exists in terms of disabling illness and accident and what might be done to restore health, to increase efficiency and prolong life. The author concludes from his studies that the costs of sickness and accidents is a social problem ranking next to unemployment in importance, and in spite of all reasonable prevention, will remain a major problem.

The various forms of compulsory health insurance which are now in force in nearly all European countries are reviewed. The compulsory health insurance movement in the United States is then considered and a plan of health insurance for this country is suggested by the author. Professor Millis believes that "it is certain that compulsory health insurance will soon become a real issue in this country unless the existing legislation relative to old age and unemployment insurance is declared unconstitutional, or rapid advance is made in solving the problem of medical care upon a more acceptable basis."

He agrees with the statements that "without the coöperation of the medical profession, no system of practice can succeed" and "that more than 80 per cent of all the ailments for which people seek medical aid can be treated most cheaply and most satisfactorily by a family physician with what he can carry in a handbag." He suggests, therefore, that some plan of insurance should be devised which is limited in its scope to the major illnesses requiring hospitalization, elaborate study and specialist treatment. It is in such cases that there is urgent need of distributing costs. They constitute a relatively small percentage of the total, but account for approximately half of the outlays for medical care. The problems involved in such a plan are considered, and other parts of a comprehensive scheme for meeting in considerable measure the problem of sickness in the United States are briefly discussed.

The problem of medical care in this country is composed of economic, social and medical elements. The medical profession should therefore welcome contributions from their more theoretical collaborators among the economists and sociologists in attempts to solve these problems, especially as these collaborators are apt to weigh evidence more impartially and with more detachment than is usually possible by members of the medical profession. This contribution by Professor Millis is a clear, brief statement of a very complex problem, and a well thought out and constructive criticism of much that has been done and written on the subject. It is to be highly commended to those who have an interest in the health of the American people, of whom the members of the medical profession must take first place.

G. R.

THE HISTORY OF THE ACUTE EXANTHEMATA. The Fitzpatrick Lectures for 1935 and 1936 delivered before the Royal College of Physicians of London. By J. D. ROLLESTON, M.A., M.D., F.R.C.P., F.S.A., Medical Superintendent, Western Fever Hospital, London. Pp. 114; illustrated. London: William Heinemann (Medical Books), Ltd., 1937. Price, 7s 6d.

CLOSELY associated with the acute exanthemata for 35 years at the Western Fever Hospital of London and long productively interested in the historic aspects of medicine, the author is well qualified to discourse on the

five diseases that comprise his subject. Smallpox, chickenpox, scarlet fever, measles and German measles are not only the most important acute exanthemata, but have the longest and most interesting history. Though known from ancient times, they have only been recognized as separate entities in surprisingly recent times, while their specific causative agents still remain in more or less obscurity. The ten portraits, which extend from Rhazes to Koplik, indicate the chronologic period covered; one regrets, by the way, that their provenance is not given. Clinicians, pediatricists, dermatologists, and all students of medicine should find satisfaction in this book.

E. K.

THE PHYSIOLOGICAL BASIS OF MEDICAL PRACTICE. A University of Toronto Text in Applied Physiology. By CHARLES HERBERT BEST, M.A., M.D., D.Sc. (LOND.), F.R.S. (CANADA), F.R.C.P. (CANADA), Professor and Head of Department of Physiology; Associate Director of the Connaught Laboratories; Research Associate in the Banting-Best Department of Medical Research, University of Toronto, and NORMAN BURKE TAYLOR, M.D., F.R.S. (CANADA), F.R.C.S. (EDIN.), F.R.C.P. (CANADA), M.R.C.S. (ENG.), L.R.C.P. (LOND.), Professor of Physiology, University of Toronto. Pp. 1684; 398 illustrations and 1 colored plate. Baltimore: William Wood & Co., 1937. Price, \$10.00.

THE distinguished author's contributions to endocrinology and experimental medicine would in themselves be sufficient to lead one to peruse this book with interest. Another item of interest therein is this latest example of a medical publishing trend, one which is especially noticeable in this country. More and more frequently do we see linked together in fresh combinations the old stereotyped subdivisions of medicine—in this case physiology, which is recognized as a science in its own right, and internal medicine. And so should they be, when it is recognized that much of today's physiology is either functional pathology or "medicine," much of today's pathology is abnormal physiology or medical etiology, pathogenesis and symptomatology; while biochemistry, from this point of view, is nothing but physiology or pathology. The point need not be labored further.

The present work, aiming to link together the laboratory and the clinic, regularly interprets the functional disturbances of common pathologic conditions. On the whole the interpretations are sound and satisfying and furnish, as the title states, a "Physiological Basis for Medical Practice." The reader will find discussions of such important symptoms and syndromes as polyuria, uremia, dyspnea, acidosis, edema, cyanosis, wound-shock, hemorrhage, hypertension, fever, etc., and of disease entities such as pneumonia, Bright's disease, various kinds of anemia and leukemia, angina pectoris, bronchiectasis and of many others.

The Reviewers are agreed that in the main the text is accurate and reliable and the selection of material judicious, with a wise elimination of unimportant work. Such linking of the resources of the clinical wards and physiologic laboratories cannot be otherwise than stimulating both to medical undergraduates and practitioners.

Having thus expressed our admiration for a noteworthy addition to medical literature, we may be permitted a few adverse criticisms. For instance, the blood and spleen chapters seem inadequate and not always exact: The spontaneous rhythmic contractions of the spleen are an old story and its reservoir function was known long before Barcroft and his party discovered it "more or less by accident;" the pale centers of the Malpighian follicles are rarely if every "germ centers;" many will not agree that experimental splenectomy "has yielded little definite information," or that clinically it should be limited to the diseases mentioned. Other instances need not be enlarged upon.

The physical makeup of the book is not pleasing. The paper is so thin and transparent that illustrations, especially photomicrographs and photographs of patients, are blurred almost as badly as in the newspapers. Figures like 27 and 268, for instance, would better not be shown. The absence of blackface type deprives the reader of a legitimate aid in finding divisions of the subjects. The Bibliography at the end of the book, instead of at the end of chapters, increases the difficulty of finding readily the references that one wants in connection with the text. A large bibliography at the end of a volume, to be sure, has its advantages; but these are largely lost if the references are offered chapter by chapter. The hundred pages of references fall between two stools. They are more numerous than required to support the statements in the text and not sufficiently numerous or well chosen to constitute a satisfactory bibliography of the many subjects covered. Granted the impossibility of satisfying everyone, still one gets the impression that the authors' personal lists of references have been augmented none too thoroughly from "standard" sources.

To recapitulate, the book is well worth while in its present form; it will undoubtedly be still more so in its next edition. E. K., B. L., I. Z.

PHYSIOLOGY IN HEALTH AND DISEASE. By CARL J. WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. Pp. 1124; 191 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, \$9.00.

As stated by the publishers: "The discussions of many topics which were treated but briefly in the first edition have been expanded, including the biophysical principles, special senses, neurohumoral agents, pain and pulmonary affections. . . . Clinical material has been used in the discussion of physiological principles and the facts and conceptions established by experiment are applied to the analyses of clinical conditions."

This new edition contains well organized, well written, important information for the study and understanding of physiology in its relations to modern clinical medicine. The material is so organized as to make essential facts readily accessible. The book presents a happy combination of fundamental principles and practical applications. E. K.

AN INTRODUCTION TO MEDICAL SCIENCE. By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S. (CANADA), Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg, Canada. Pp. 307; 108 illustrations. Philadelphia: Lea & Febiger, 1937. Price, \$3.50.

This department has often, and rightly, decried the use of short compends and textbooks abbreviated in an attempt to suit the modest demands and limited time of the medical student. Much better is it for him to own an adequate textbook that he has perforce become acquainted with, and that he can refer to later, even if he has not been able to read it from cover to cover during his medical school course. Approval of the present, volume, however, is not in the least inconsistent with the above viewpoint. As the author says in his Preface, "A little knowledge is a dangerous thing, but not if you know how little it is." (This, by the way, seems to the Reviewer to constitute an aphorism well worth permanent preservation in our literature.) Certainly, the nurse, technician and premedical student for whom the book is chiefly intended should not be in danger of thinking that they have acquired sufficient knowledge of the subjects treated to

equip them for their life work. On the other hand, presented by one who knows his subject and who is able to write clearly and forcibly about it, this little book gives perspectives of correlations between lesions and symptoms that often permit a better comprehension of the essential processes of disease than is possible in the necessarily more detailed conventional textbooks. One who is contemplating or beginning medical studies, or a patient who wishes to understand more about himself must often wonder "what it is all about, not seeing the wood for the trees," again in the words of the Preface. This attempt should put him on the right track.

The greater part of the book follows the conventional plan of a textbook of pathology: Part I, General Principles on the nature and various causes of disease, and general body reactions (*i. e.*, Etiology and General Pathology); Part II, diseases of different parts of the body, considered in much the same order as in Special Pathology, but in quite a different way. A short Part III, Practical Applications, deals with the Prevention of Disease and the Nurse and the Laboratory.

We hope that the book will be widely disseminated among those whom it is designed to serve. We know of none that supplies this real need as well as this one does.

E. K.

A HAND-BOOK OF OCULAR THERAPEUTICS. By SANFORD R. GIFFORD, M.A., M.D., F.A.C.S., Professor of Ophthalmology, Northwestern University Medical School, Chicago; Attending Ophthalmologist, Passavant, Wesley Memorial, Evanston and Cook County Hospitals. Pp. 341; 60 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, \$3.75.

THE demand for this excellent text on Ocular Therapeutics has necessitated a second edition, which includes a number of new procedures that have appeared in the literature in the past 4 years. It is an extremely useful book for both the general practitioner and the ophthalmologist.

F. A.

ENDOCRINOLOGY. CLINICAL APPLICATION AND TREATMENT. By AUGUST A. WERNER, M.D., F.A.C.P., Assistant Professor of Internal Medicine, St. Louis University School of Medicine; Associate Physician, St. Mary's Group of Hospitals, etc. Pp. 672; 265 illustrations. Philadelphia: Lea & Febiger, 1937. Price, \$8.50.

THIS clinical endocrinology is written in a direct, lucid manner, and describes the underlying physiological principles in a way that is adequate for an understanding of diseases and their treatment. Many case histories are given of illustrative types. It should be a very useful book for the general practitioner. It is a very scientific, clinical presentation of endocrinology, almost completely eliminating endocrine fantasies, and containing few individual viewpoints on which the Reviewer would differ.

In a book of this type, it would seem better to omit some of the descriptions of uncorroborated and debatable publications, pathological conditions not proved to involve endocrines and experimental work not directly applicable to human disease; because if such matters are discussed, it would seem advisable to present them in all their intricacies from all standpoints, and that can be done only in large systems or in books on separate endocrine organs. In a single volume on all endocrines, errors of omission would seem preferable. However, the space allotted to such matters is very small and theories and personal views are clearly separated from concrete facts; consequently no intelligent reader should be confused.

The physical makeup of the book is very attractive. It should fill a real need in treating of clinical endocrinology in the compass of a single volume.

I. Z.

DISEASES OF THE NEWBORN. By ABRAHAM TOW, M.D., Adjunct Professor of Pediatrics, New York Polyclinic Hospital and Post-Graduate Medical School; Assistant Adjunct Pediatrician of the Abraham Jacobi Division for Children of the Lenox Hill Hospital, etc. Pp. 477; 53 illustrations. New York: Oxford University Press, 1937. (No price given.)

THIS volume offers mainly a rather adequate digest of the literature pertaining to those conditions affecting the newly born infant. The subject matter is almost entirely presented in an impersonal way—most of the treatments resembling the brief abstracts to be found in the abstract section of a journal. Unfortunately there are very few references to the author's experiences and no analyses of cases or groups of conditions and results which might have been included for the sake of prognosis. Other recent volumes concerned with the New Born period have been less encyclopedic but have evinced more originality of treatment and have offered far more in the way of personal experience. It is significant that practically all of the illustrations are drawn from the literature. The author adopts a sound, conservative position on all debatable matters. This is to be commended but the didactic statements would be more forceful if supported by case analyses and hospital statistics. E. T., Jr.

A HUNDRED YEARS OF MEDICINE. By WYNDHAM E. B. LLOYD, M.A. (CANTAB.), M.R.C.S. (ENG.), D.P.H. (ENG.). Pp. 344. London: Gerald Duckworth & Co., Ltd., 1936. Price, 15/.

THIS is one of Duckworth's 100-year series, other volumes having already appeared on Psychology, Inland Transport, Anthropology and English Government. In the first part is presented the study of medicine 100 years ago; in the second and longest, the scientific discoveries of the past century, and in the third, the organization of public health. The author was obviously faced with such unmanageable abundance of material, that he feared unwieldy details on the one hand, unreadable excessive condensation on the other. He therefore determined on arbitrary selection of those items that would be more interesting to and easily understood by the English layman and appears to have selected wisely. Anyone who has digested this book will be well informed on the progress of medicine in the past century. E. K.

TRAUMA AND DISEASE. Edited by LEOPOLD BRAHDY, B.S., M.D., Physician in Charge of Industrial Diseases and Accidents in the Office of the Corporation Counsel of the City of New York, and SAMUEL KAHN, B.S., M.D., Medical Examiner in the Bureau of Workmen's Compensation of the Department of Labor, State of New York, New York City (25 Contributors). Pp. 613; illustrated. Cloth \$7.50. Philadelphia: Lea & Febiger, 1937. Price, \$7.50.

THIS book is timely in view of the increasing compensation given to workers injured during their work and the increasing awards made for liability accidents. The editors have written from their extensive experience the first chapter on trauma in the etiology of disease. Thereafter follow 16 chapters by men who are outstanding in their field, each discussing trauma in its relation to disease in a single part of the body. For example the chapter on trauma and heart disease, written by P. D. White and R. E. Glendy, discusses the general principles, etiologic relationships, structural changes and disorders of function of the heart resulting from trauma. Then follows a series of illustrative cases with a brief but comprehensive discussion. Various authors have appended bibliographies.

The book is excellent as a reference for those who are confronted with the problems of the relationship between trauma and disease. It should be invaluable to physicians dealing with compensation or liability insurance. It is undoubtedly the outstanding work of its kind. L. F.

THE PSYCHOLOGY OF EATING. By LEWIS ROBERT WOLBERG, M.D. Pp. 321. New York: Robert M. McBride & Co., 1936. Price, \$3.00.

THE author, a psychiatrist at King's Park State Hospital, New York, who also lectures to the nurses there on dietetics, begins his preface with no mean claim. He states that the book "Is a complete scientific system of eating which discusses the need for a new dietary point of view. It is a book which reviews comprehensively medical, social and psychological aspects of diet. It is a practical book which will help every normal person to construct a balanced menu for the utmost enjoyment of health and efficient living. And it will permit one to secure new standards in dietary efficiency without sacrifice or self-deprivation, without robbing oneself of the zest and appetite pleasures inherent in good foods." Written directly to the prospective dietist, the book records many sound observations and reflections in commonly understandable terms and in an easy style, reminiscent of some American anti-faddist literature. Guided by the principal "Because science speaks an unknown tongue many people fall victims to the blandishments of the food faddist," the author gives concrete rules for dieting in overweight and underweight and in various disease conditions; but always with a sufficient background of *raison-d'être* to appeal to the intelligent. E. K.

CATARACT. ITS PREVENTIVE AND MEDICAL TREATMENT. For Specialists, General Practitioners and Students. By A. EDWARD DAVIS, A.M., M.D., Formerly Professor of Ophthalmology, New York Post-Graduate Medical School and Hospital (Columbia University), etc. Pp. 161; 11 charts. Philadelphia: F. A. Davis Company, 1937. Price, \$3.00.

It is unfortunate that the statistics reported in this book, to substantiate the author's claim for the successful use of lens-protein in the treatment of cataracts, are not convincing. Until the treatment has received confirmation by other workers, it hardly merits presentation in the form of a book. F. A.

NEW BOOKS.

The Normal Encephalogram. By LEO M. DAVIDOFF, M.D., Assistant Professor of Neurology in the College of Physicians and Surgeons, Columbia University; Attending Neurological Surgeon to the Neurological Institute of New York, and CORNELIUS G. DYKE, M.D., Assistant Professor of Radiology in the College of Physicians and Surgeons, Columbia University; Assistant Director, in the Department of Radiology of the Neurological Institute of New York, New York City. Pp. 224; 149 illustrations. Philadelphia: Lea & Febiger, 1937. Price, \$5.50.

Failure of the Heart and Circulation. By TERENCE EAST, M.A., D.M., F.R.C.P., Physician, King's College Hospital and Woolwich Memorial Hospital. Pp. 130. London: John Bale, Sons & Curnow, Ltd., 1937. Price, 2/6d.

Public Medical Services. A Survey of Tax-supported Medical Care in the United States. By MICHAEL M. DAVIS. Pp. 170. Chicago: The University of Chicago Press, 1937. Price, \$1.50.

The Patient and the Weather, Vol. IV, Part 1. By WILLIAM F. PETERSEN, M.D., with the assistance of MARGARET E. MILLIKEN, S.M., Organic Disease. Cardio-vascular-renal Disease, including a Chapter on Experimental Endocarditis by ALEXANDER J. NEDZEL, M.D., Associate Professor in the Department of Pathology, Bacteriology and Public Health, University of Illinois, College of Medicine, Chicago. Pp. 663 (lithographed); 443 illustrations. Ann. Arbor: Edwards Brothers, Inc., 1937. Price, \$10.00.

Physicians and Medical Care. By ESTHER LUCILE BROWN, Department of Statistics, Russell Sage Foundation. Pp. 202. New York: Russell Sage Foundation, 1937. Price, 75c.

Clinical Reviews of the Pittsburgh Diagnostic Clinic. Guideposts to Medical Diagnosis and Treatment. Eight Contributors. Edited by H. M. MARGOLIS, B.S., M.D., F.A.C.P. Pp. 552; 6 figures, 5 charts and 4 tables. New York: Paul B. Hoeber, Inc., 1937. Price, \$5.50.

Síndromc Adiposo-Genital. By DR. LUIS VÍAMONTE CUERVO. Pp. 62. Habana: Seoane, Fernández Cía, 1937.

Dr. Bodo Otto and the Medical Background of the American Revolution. By JAMES E. GIBSON. Pp. 345; illustrated. Springfield, Ill.: Charles C Thomas, 1937. Price, \$4.00.

The International Medical Annual. Fifty-fifth Year, 1937. A Year Book of Treatment and Practitioner's Index. Thirty-four Contributors. Editors: H. LETHEBY TIDY, M.A., M.D. (Oxon.), F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S. Pp. 605; 89 text illustrations, and 68 plates (some in color). Baltimore: William Wood & Co., 1937. Price, \$6.00.

The Practice of Ionization. By J. NEWTON DYSON, M.R.C.S. (Eng.), L.R.C.P. (Lond.). With a Foreword by ELKIN P. CUMBERBATCH, M.A., B.M. (Oxon.), D.R.M.E. (Camb.), F.R.C.P. Pp. 178; 9 illustrations. London: Henry Kimpton, 1936. Price, 6/.

NEW EDITIONS.

A Textbook of Embryology. By HARVEY ERNEST JORDAN, A.M., Ph.D., Professor of Histology and Embryology, University of Virginia, and JAMES ERNEST KINDRED, M.A., Ph.D., Associate Professor of Histology and Embryology, University of Virginia. Pp. 613; 473 text illustrations, 33 plates. Third Edition. New York: D. Appleton-Century Company, Inc., 1937. Price, \$6.50.

Important in this edition are many improved illustrations and textual additions under the topics of hemopoiesis, lymphatics, lung, sex determination, and anomalies.

Mikromethodik. Quantitative Bestimmung der Harn-, Blut- und Organbestandteile in Kleinen Mengen für Klinische und Experimentelle Zwecke. By LUDWIG PINCUSSEN. Pp. 193; 31 illustrations. Leipzig: Franz Deuticke, 1937. Price, M. 5.

PROGRESS OF MEDICAL SCIENCE

SURGERY.

UNDER THE CHARGE OF
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NITROUS OXIDE-OXYGEN ANESTHESIA AND ANOXIA.

NITROUS oxide-oxygen has been generally considered as one of the safest of anesthetic agents. It is because of this that it has been commonly employed for patients whose condition is not especially good. It has, in fact, often been used as the anesthetic of choice in "bad risk patients." It has frequently been employed in the presence of hypotension, either acute or chronic, for it has been generally taught that nitrous oxide and oxygen anesthesia causes a rise in the systolic blood pressure. Even if this does occur, the resultant effects may be such as seriously to impair functions which may already have been impaired by the lesion requiring anesthesia and operation. The frequent casual suggestion for "just a whiff of gas" indicates a lack of consideration for the possible dangers in the use of this gas. Its use is widespread for minor surgical conditions as well as in situations where it is difficult to watch the patient such as in fluoroscopic reduction of fractures and in obstetrical practice.

That this anesthetic is not as safe as most of us have believed is now becoming apparent. The dangers from nitrous oxide have been stated frequently.^{1-3,5,6,8,10,12,15,17,18,23,31} The most important are those associated with anoxemia. The induction of the anesthetic state with nitrous oxide depends largely, if not completely, on the production of anoxemia with a resulting decreased oxygenation of the tissues. Henderson, Brown and Lucas,¹⁶ Leake and Hertzman,¹⁹ and Greene and Curry¹⁴ have indicated that the anesthetic effect of nitrous oxide is due chiefly to the anoxemia which it causes. That there may be some

narcotic effect is not denied, but it is a well known fact that in order to get deep anesthesia with nitrous oxide and oxygen, it is necessary to decrease the oxygen concentration to a level at which definite cyanosis is apparent. After a period of anoxemia, however, it is frequently possible to maintain fair anesthesia with a decreased concentration of nitrous oxide. Even at this period, however, the concentration of oxygen which can be used and still maintain anesthesia with moderately efficient relaxation is at the critical level for oxygenation of tissues and below the concentration normally available to the organism in the air. Greene and Curry¹⁴ concluded that anesthesia with nitrous oxide and oxygen depended more on the decrease in saturation of oxygen in the blood than on increase of saturation of nitrous oxide. Henderson, Brown and Lucas¹⁶ tested the concept of Bert⁴ and Martin²² that nitrous oxide alone could produce anesthesia if the pressure were increased, but were unable to verify the conclusions of these authors. Henderson and his associates¹⁶ placed rabbits in a specially constructed tank containing a mixture of 84% nitrous oxide and 16% oxygen at a pressure of 2 atmospheres without producing anesthesia.

Anoxemia is, as is well known, commonly associated with nitrous-oxide-oxygen anesthesia. When the patient is kept "pink," as Yandall Henderson has insisted he should be, unless there is an associated anemia, the dangers from this gas mixture are minimized. The difficulty of maintaining a good color and obtaining the required depth of anesthesia is obvious. Despite the fact that the average surgeon looks upon cyanosis as a warning sign that the patient is receiving too little oxygen, there are those who feel that cyanosis, during nitrous oxide-oxygen anesthesia, is not only to be expected but is necessary.²¹ Raginsky and Bourne,²⁶ however, state that it is possible to produce anesthesia in man without cyanosis. In addition to the anoxemia from nitrous oxide-oxygen anesthesia, there is usually an additional anoxia resulting from the pre-operative administration of depressant drugs. The use of morphine pre-operatively has become nearly universal. Morphine is known to depress respiration. In addition to its depressant action on pulmonary ventilation, morphine has a tendency to produce tissue anoxia. Not only does morphine tend to depress oxygenation in the organism, but Shute and Davis²⁸ demonstrated that morphine given to mothers had an asphyxial effect on the newborn infant and scopolamine supplemented this action.

There are additional methods by which the anoxemia of nitrous oxide and oxygen anesthesia may still further affect function. The stimulation of the medullary centers by oxygen want may slow cardiac activity and increase peripheral vasoconstriction. The increased peripheral resistance may impede blood flow and lead to a further oxygen deficit to the tissues. This may be especially true when the original condition requiring anesthesia has already seriously influenced blood flow in the periphery. The cumulative effects of an oxygen deficit from an impaired blood flow prior to anesthesia, and a further reduction during anesthetization with a mixture providing an insufficient or minimal amount of oxygen may be sufficient to cause a serious breakdown of normal functions.

Many reports of deaths during nitrous oxide-oxygen anesthesia are

to be found in the literature. That less sudden, but often as serious effects may follow anesthetization is not so generally recognized. That following nitrous oxide-oxygen administration certain disorders such as hysteria, coma, disorientation and various motor disturbances occurred has long been known. In fact, in his work, published in 1800, Sit Humphrey Davy⁹ reported the following: "That single doses, nevertheless, are capable of producing permanent effects in some constitutions is evident, as well from the hysterical cases as from some of the details, particularly that of Mr. M. M. Coates." The detail referred to is a description of the subjective effects on Mr. Coates after breathing nitrous oxide and indicated that Mr. Coates was quite irritable and unsteady, so much so that for 6 or 7 days he was handicapped in his work and was mildly hyperexcitable for over a fortnight.

Undoubtedly, should one very carefully study postanesthetic cases, with the thought of learning of minor nervous disorders, it is quite likely that many could be found to be related to the anesthesia, and it is quite possible that many unexplained deaths might be attributed to the anesthetic agent.

The most carefully studied series of cases with regard to sequelæ of nitrous oxide-oxygen anesthesia is that of Courville.⁷ In a series of 9 cases which terminated fatally, Courville was able to find evidence, by a study of microscopic sections, of definite cerebral cell damage. The damage consisted of degenerative cortical changes of varying degree. During anesthesia in most of the cases there was some difficulty, either in the nature of deep cyanosis or a period of respiratory arrest. The postoperative symptoms were somewhat varied, but hyperthermia was present in all the cases which terminated fatally. Motor weakness, coma, convulsions, flaccidity, and increase in respiratory rate were common findings. The postanesthetic survival period varied from 40 hours to 26 days.

In addition to the 9 cases which died, Courville⁷ also reported 4 cases which recovered, 2 completely, and 2 in which residual mental changes persisted.

In 2 of the instances a definite defect was found in the machine which was used for administering the gas mixture so that no oxygen was given, and in other instances, the gas used contained an excess of free nitrogen. The importance of an efficient apparatus and the highest purity of the gas mixture is, therefore, of the greatest importance.

The cases reported by Lowenberg, Waggoner, and Zbinden,²⁰ and by Schreiber and Gates²⁷ were quite similar to those of Courville.⁷ The postanesthetic sequelæ were so much like those of Courville that there can be no doubt but that the mechanism was a similar one. These three papers, we believe, are of the greatest significance and should be read by all those who still believe that this gas mixture is the safest anesthetic in the hands of the professional anesthetist.

The possible cause of these disturbances is to be sought in anoxemia of the brain tissue. Added weight is given to this concept by the work of Gildea and Cobb,¹³ who in experimental animals produced brain lesions similar to those found by Courville in his patients. Apparently, it is necessary that a greater insult be given than is offered by the anoxemia from a carefully administered uneventful nitrous oxide-oxygen

anesthesia. Either the oxygen unsaturation must be extreme as in the cases where pure nitrous oxide was given, or where respiratory difficulties ensued; or the ability of the tissues to utilize oxygen must be impaired; or the actual oxygen carrying apparatus must be at fault, as in cases with anemia; or the ability of the pulmonary tissue to transfer oxygen must be defective, as in Courville's first case who had a lung abscess, as well as in one in the series of Lowenberg, Waggoner and Zbinden; or the reduction in the blood flow must be so great as to lead to a serious oxygen deficit. The possibility of materials other than nitrous oxide having been administered as impurities is, of course, present. Free nitrogen as an impurity should tend only to increase the anoxemia. If other impurities were present which might act similarly to carbon monoxide in binding available hemoglobin, a train of events such as described by Courville,⁷ Lowenberg, *et al.*,²⁰ and Schreiber and Gates²⁷ might ensue. We know of no suggestion that nitrous oxide will form a stable compound with hemoglobin. Should nitric oxide be present, such a compound would form. Nitric oxide hemoglobin is quite stable and has been shown by Drabkin and Austin¹¹ to give a curve similar to carbon monoxide hemoglobin when studied spectrophotometrically. The possibility of saturation with nitric oxide, if such were present, would be increased during phases of oxygen lack, since in the presence of oxygen, higher oxides of nitrogen would be formed. These oxides are likewise toxic, and are irritating. Pfesser²⁵ found that nitric oxide was toxic in smaller doses than the dioxide so that when nitric oxide was administered as an impurity, adequate oxygen would act to reduce the toxicity. Nitric oxide might be expected to be formed in the preparation of nitrous oxide from ammonium nitrate, and carbon monoxide likewise is a possibility if organic impurities are present in the ammonium nitrate.²⁹ Not only is the formation of nitric oxide a possibility, but Palkin²⁴ reports the presence of this compound in small amounts in samples of nitrous oxide tested by the Bureau of Chemistry of the United States Department of Agriculture. The actual amount of nitric oxide necessary to produce toxic effects need not be great if there is already deficient oxygenation, since the action of this compound would be expected not only further to decrease the oxygen-carrying capacity but to depress the tissue respiration as well.

Whether the sequelæ of nitrous oxide-oxygen anesthesia reported by Courville,⁷ Lowenberg, Waggoner and Zbinden,²⁰ and Schreiber and Gates,²⁷ are due to lack of oxygen or to a toxic substance in the gas mixture is an unsolved problem. Were it not for the occasional case in which the period of anoxemia is very short, the relationship between anoxemia and the brain injury found might be adequate to explain the difficulty. Marked anoxemia and arrest in respiration are not uncommon, yet the occurrence of brain damage is rare even after a stormy anesthetization. The relationship of blood flow, especially cerebral blood flow during the period of anoxia, must have an important bearing on the postanesthetic sequelæ. An efficient blood flow during the period of anoxia will probably offset the low oxygen saturation, while an anoxia further accentuated by an impaired blood flow will accentuate the tissue changes. The sequelæ described by the above authors are so dramatic that they cannot be overlooked, but their relationship to

anesthesia may be overlooked. Toxic materials have been found only in small amounts in commercial nitrous oxide. If anoxemia were absent during anesthesia, the toxic material which may be present, namely nitric oxide, would be less toxic if toxic at all, since it would be readily oxidized to the higher oxides. It appears quite possible that anoxemia and the toxic impurities present may combine to cause the disturbance noted by Courville,⁷ Lowenberg, Waggoner and Zbinden²⁰ and by Schreiber and Gates.²⁷

Nitrous oxide-oxygen anesthesia is frequently given under a variety of conditions, and by inexperienced anesthetists. It has been said that 97% of anesthetizations are given by individuals not medically trained,³⁰ and, of course, some of the remaining 3% are given by medical men and dentists not trained in anesthesia. The choice of the anesthetic and the method and manner of its administration are important considerations and are frequently more important than the operation which is to be done. Anesthesia has widened the scope of surgery; the willingness of many surgeons and patients to trust anesthesia to lay hands has definitely hindered the progress of anesthesia.

The margin between life and death under anesthesia is narrow enough to cause us to think seriously about the problem. Evidence of irreparable tissue damage as a result of anesthesia should indicate that we should be even more on our guard. In experienced hands nitrous oxide-oxygen is a dangerous anesthetic—the danger is surely not minimized by trusting this agent to individuals inexperienced in the physiologic, pharmacologic and pathologic aspects of anesthesia.

BIBLIOGRAPHY.

- (1.) Adams, J.: *Lancet* 1, 738, 1894. (2.) Ashford, F. A.: *AM. J. MED. SCI.*, 57, 408, 1869. (3.) Baldwin, J. F.: *Med. Rec.*, 90, 177, 1916. (4.) Bert, P.: *Comp. Rend. de l'Acad. d. Sci.*, 87, 728, 1878; 96, 1271, 1883. (5.) Caine, A. M.: *Am. J. Surg.*, 37, 34, (Suppl.), 1923. (6.) Clement, F. W.: *Anesth. and Analges.*, 7, 72, 1928. (7.) Courville, C. B.: *Medicine*, 15, 129, 1936. (8.) Davies, C. W.: *Brit. J. Anæsth.*, 8, 112, 1930. (9.) Davy, H.: *Researches Chemical and Philosophical, Chiefly Concerning Nitrous Oxide or Dephlogisticated Nitrous Air and its Respiration*, London, Johnson, 1800. (10.) Downs, T. McK.: *Ann. Surg.*, 99, 974, 1934. (11.) Drabkin, D. L., and Austin, J. H.: *J. Biol. Chem.*, 112, 51, 1935-36. (12.) Evans, J. H.: *Anesth. and Analges.*, 7, 65, 1928. (13.) Gildea, E. F., and Cobb, S.: *Arch. Neurol. and Psychiat.*, 23, 876, 1930. (14.) Greene, C. and Currey, H. M.: *Arch. Int. Med.*, 35, 371, 1925. (15.) Healy, C. W.: *Brit. Med. J.*, 2, 343, 1926. (16.) Henderson, V. E., Brown, W. E., and Lucas, G. H. W.: *Anesth. and Analges.*, 6, 21, 1927. (17.) Hewitt, F. W.: *Lancet*, 1, 1053, 1899. (18.) Kaye, G.: *Med. J. Australia*, 2, 804, 1931. (19.) Leake, C. D., and Hertzmann, A. B.: *J. Am. Med. Assn.*, 82, 1162, 1924. (20.) Lowenberg, K., Waggoner, R., and Zbinden, T.: *Ann. Surg.*, 104, 801, 1936. (21.) Macklin, A. H.: *Lancet*, 2, 897, 1931. (22.) Martin, C.: *Comp. Rend. l'Acad. d. Sci.*, 106, 290, 1888. (23.) Owen, J. G.: *Brit. Med. J.*, 2, 1635, 1904. (24.) Palkin, S.: *Anesth. and Analges.*, 6, 215, 1927. (25.) Pfesser, G.: *Arch. f. Exp. Path. u. Pharm.*, 179, 545, 1935; 181, 145, 1936. (26.) Raginsky, B. B., and Bourne, W.: *Canadian Med. Assn. J.*, 30, 518, 1934. (27.) Schreiber, F., and Gates, N.: *Nitrous Oxide Anesthesia Related to Alterations in the Central Nervous System Structures*, Read before the Detroit Academy of Surgery, February 11, 1937. (28.) Shute, E., and Davis, M. E.: *Surg., Gynec. and Obstet.*, 57, 727, 1933. (29.) Stanton, B. L.: *Med. J. Australia*, 2, 845, 1935. (30.) Troup, G.: *Ibid.*, p. 857. (31.) Yaskin, J. C.: *Arch. Neurol. and Psychiat.*, 26, 371, 1931.

OPHTHALMOLOGY.

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 THE ETIOLOGY OF RECURRENT UVEITIS. A REVIEW OF
EXPERIMENTAL STUDIES.

THE determination of the cause of an individual case of iridocyclitis or uveitis, particularly of recurrent type, is often, if not usually, extremely difficult. In the absence of definitely demonstrable syphilis, tuberculosis, or blood stream infection by staphylococci, streptococci, meningococci and the like, which latter usually produce single and not recurrent attacks of uveitis, the ocular disease is usually ascribed, in this country at least, to focal infection. At times these foci of infection can be demonstrated readily, and their removal has a favorable effect on the course of the ocular disease. At other times no obvious foci can be found. At times removal of foci and treatment with specific, autogenous, or nonspecific vaccines has little permanent effect on the course of the disease or on its recurrence. The reasons for this failure of therapy are not clear. In any case of uveitis, whether due to syphilis, tuberculosis, or focal infection, the mechanism of the recurrent attacks is not well understood. In some cases of syphilitic and tuberculous uveitis, the specific organisms can be demonstrated in the tissues of the eye. In most cases, however, organisms cannot be found in the ocular tissues.

In the early years of the theory of focal infection, various workers attempted to demonstrate the bacterial metastatic character of iritis and uveitis. In 1915, Rosenow¹² reported that, in a large group of animals injected intravenously with various organisms, particularly strains of streptococci, 48 animals had developed lesions of the eyes. He stated: "It must not be supposed that the occurrence of these lesions is accidental because they appear to occur commonly only after injections of strains as isolated in rheumatic arthritis and myositis (17%) and in herpes zoster (15%) while after injections of strains from appendicitis, ulcers of the stomach, cholecystitis and erythema nodosum, eye lesions are extremely rare." Rosenow then proposed his theory of "elective localization" of streptococci in which it is assumed that, under certain conditions of growth in foci or in culture, the streptococci develop "specific affinity for certain tissues."

Experimentally, iritis can be produced in animals by the direct injection of organisms into the anterior chamber. According to A. L. Brown, Koske in 1905 produced ocular inflammation in rabbits by injecting into the anterior chamber living *B. subtilis*, *B. prodigiosus*,

and staphylococci. Iritis will also occur in the homolateral eye following the injection of pathogenic organisms into the internal carotid artery. Iritis develops at times also after intravenous injection of living bacteria, as demonstrated by Rosenow and others. Brown states that it has been reported also after the intravenous administration of yeasts (Stoch), of filtrates of ferment-producing bacteria (Guillery), and of toxin from *B. prodigiosus* (Wood). Benedict states that Brown and Irons produced iritis in rabbits by intravenous injections of streptococci, *B. mucosus capsulatus* (Friedländer), *B. pyocyaneus*, and gonococci, as a result of which they concluded that bacteria reach the eye through the circulating blood and can be recovered from the eyes in which iritis has occurred. It was necessary, however, to inject sufficient organisms to produce a septicemia.

Apparently, it was not until after the reports of Rosenow in 1914 and 1915 that attempts were made to utilize, for experimental intravenous injections, organisms derived from humans with iritis or uveitis. In 1916, Irons, E. V. L. Brown and Nadler⁸ reported the results of intravenous injections into rabbits of hemolytic streptococci cultured from a chronic dacryocystitis in a patient with acute iritis. Typical iridocyclitis developed in 3 of 4 animals injected. Organisms obtained from the sac one month later caused iritis in 2 of 4 rabbits. Later cultures from the sac failed to cause iritis in any of 22 rabbits injected. Apparently, "the invasive power of the organism for special tissues" had been changed during residence in the focus, as it was proved to be changed in animal passage and also in subcultures.

In 1919, Lewis¹⁰ reported the production of iritis in a rabbit by the injection into the blood stream of a culture of *Streptococcus viridans* grown from a periapical infection in a patient with acute iritis. The same organism was recovered on culture of a section of the rabbit's iris. Lewis stated: "This experiment proves absolutely for the first time, as far as I know, the selective affinity of the organisms found in dental root abscesses for the special structure which had been affected in the individual from which the tooth was taken."

In 1921, Meisser and Gardner reported the experimental production of iritis in rabbits through two animal passages with a streptococcus isolated from an infected tooth in a case of acute iritis. Benedict,² in 1921, studied the effects of the intravenous injection into rabbits of green-producing streptococci obtained from foci of infection in 14 patients with iritis and uveitis. Five of the patients had acute iritis. Organisms obtained from 4 of these 5 patients produced iritis in rabbits. Nine of the patients had chronic and recurrent iritis or chronic uveitis. Organisms obtained from these patients failed to produce iritis in rabbits. He stated his belief "that iritis is produced by bacteria arising from foci of infection around the roots of teeth and in the tonsils, that it is an inflammatory reaction brought about by the presence of bacteria in the tissues of the iris carried to the iris by the blood stream from the foci of infection, that such bacteria have the ability to grow and do grow in such environments." He stated further: "Iritis of focal infection origin is a myositis caused by an organism that at some period of its growth may cause iritis and at other periods inflammation of some other muscle. . . . This affinity for iris tissue becomes a function of the organism spontaneously or may be acquired by growing on

iris tissue . . . this affinity for the iris is easily lost by the organism when grown in different environments . . . it will change its affinity for special structural tissue or even lose its virulency to a marked extent." The possibility of the streptococcus acquiring an affinity for the uveal tract by growing on iris tissue is disputed by Brown, who found that growing the streptococci in uveal tissue attenuated the virulence of the organism for the uveal tract, though he states that Zanettin obtained the opposite result.

In 1923, Haden⁷ reported that lesions of the eyes occurred in 68% of 66 rabbits injected intravenously with freshly isolated cultures of streptococci obtained from the teeth of patients suffering from metastatic infections of the eye. In a control group of 169 rabbits injected with cultures obtained from patients without eye lesions, inflammation of the eyes developed in only 14.8%. Haden stated also that he had noted recurrent attacks in the injected rabbits.

In 1927, in summarizing his experiences of many years in the study of focal infections, Rosenow^{12a} stated with particular reference to lesions of the eye: "Relief from symptoms following removal of foci of infection, while good evidence of causal relationship, still leaves open the question whether the lesions in the eye were the result of localization of bacteria or of their toxins only. Materials for cultural and microscopic study are not obtainable, and, judging by experimental findings, even if the fluid in the anterior chamber were aspirated, it would likely be sterile when living organisms were present in the affected tissues. Systemic reactions are slight, cultures from the blood are negative, antibody production is minimal, and hence the usual agglutination reactions with suspected organisms are of little or no diagnostic value." With reference to his experimental work, he said: "Localization of the bacteria in the eye may sometimes be accidental and a part of other disease manifestations. However, the animal experiments, now amply corroborated, indicate clearly that localization and growth in most instances are due to peculiar, acquired or inherent, properties of the bacteria themselves and to their power to localize electively and that this is in part due to the production of a toxin or poison which affects specifically the tissues in which localization and growth occur. . . . Among the microorganisms isolated which manifested the greatest elective localizing power and with which the common forms of diseases of the eye have been reproduced, is a streptococcus which usually produces greenish or slightly hemolytic colonies on blood agar, which requires a reduced oxygen tension for its isolation, and from which autogenous therapeutic vaccines, of great value in many cases, have been prepared. . . . The experimental results indicate clearly that lesions in the eye which are associated with exudation, even though slight, are usually due to actual localization of microorganisms, while the milder manifestations may sometimes be due to absorption of toxins which are formed in the focus or elsewhere and reach the eye in the blood stream."

In 1932, Rosenow and Nickel¹³ presented a statistical study of a large series of cases of experimental iritis in rabbits produced by the intravenous injection of streptococci obtained from human foci of infection. Two hundred and seventy-two rabbits were injected with freshly isolated streptococci obtained from foci of infection in 87 patients

with acute, chronic, primary or recurrent attacks of iritis, iridocyclitis and uveitis. Of these rabbits 41.6% developed eye lesions; 5% developed lesions in the joints. Ocular localization occurred in only 0.4% to 1.9% of rabbits injected with streptococci obtained from foci of infection in patients with miscellaneous diseases without lesions in the eyes. Of the rabbits injected with organisms obtained from patients with acute iritis 75% developed ocular lesions. In a series of 215 rabbits, it was found that organisms obtained from the tonsils localized in the eyes in 67%, organisms from the teeth in 53%, from the cervix in 50%, and from the prostate in 40%. Streptococci could be demonstrated in the tissues and could be recovered in cultures and these organisms again reproduced the lesion in other rabbits. However, they lost their specificity after 3 or 4 animal passages or subcultures. It was found that various strains of streptococci have characteristic cataphoretic velocities or electrical potentials which correspond closely to their specific localizing characteristics, so that it can be predicted from this test where the organisms will localize after intravenous injection. Rosenow has been able to produce hyperimmune sera in horses which give specific skin reactions and which can be used to produce immunity in patients harboring the specific strain of streptococcus.

More closely to reproduce experimentally the conditions found in man, Rosenow and Nickel infected the teeth of 7 dogs with four strains of streptococci obtained from patients with iritis. Three of these dogs developed a primary inflammatory reaction in the eyes, but recurrent inflammation did not occur during periods of observation of from 4 months to 3 years. In one dog, the teeth were infected on two separate occasions. Iritis developed after the second inoculation but not after the first. This result was interpreted as an indication that the eyes had become allergic to the streptococci.

The experiments carried out by these several workers seem to indicate clearly that inflammations of the uveal tract can be caused by direct bacterial metastasis to the eye, that certain strains of streptococci are more apt than others to cause ocular inflammations, and that the same strain of streptococcus at different times or growing under different conditions may have a greater or less tendency to localize in the eye. The fact remains, however, that these experiments do not furnish the complete answer to the problem of recurrent uveitis in man. The iritis and uveitis produced experimentally are not identical clinically or histologically with human iritis and uveitis, and it has not been possible to cause spontaneously recurrent inflammations of the eyes in animals even by the establishment of foci of infection in the teeth or elsewhere.

Because of these manifest defects in the experimental proof of repeated bacterial implantations in the eye as the explanation of recurrent human uveitis, A. L. Brown was attracted to the possibilities of the allergic theory of recurrent iritis and uveitis. Two methods of producing ocular anaphylaxis have been known for some time: 1, introducing foreign proteins, bacteria, or toxins into the eyeball and giving intravenous injections of the same substance after the sensitizing period, or 2, producing general sensitization by intravenous injection and then injecting the same material into the eye at a later period. A. L. Brown quotes a number of early experiments: In 1908, Nicolle and Abt demonstrated the local sensitization of ocular tissues. They sensitized guinea

pigs by intraperitoneal injections of serum and produced ocular inflammation by injection of the same serum into the anterior chamber 32 days later. In 1910, Krusius produced general sensitization in guinea pigs by intraocular injection of cow serum. Also, he sensitized guinea pigs by subcutaneous injections and later produced ocular inflammation by anterior chamber injection of the same material. Kummel, in 1910, and Wessely, in 1911, sensitized one eye to foreign serum and then were able to produce ocular inflammations in the other eye by injections of the same serum. Woods, in 1916, sensitized animals by intraperitoneal injection of foreign protein and later perfused the heads with the same antigen and caused contraction of the pupils and small hemorrhages in the fundi. In 1919, Wibaut produced intraocular inflammation by injection of foreign protein into the vitreous 17 days after a preliminary injection of the same protein.

These various experiments demonstrated the possibility of producing allergic reactions in the eyes of animals. Considerable light was thrown upon the nature of these reactions by the studies of Derick,⁵ Swift¹⁵ and Andrews,¹ and of the Seegals.^{14a,b} In 1926, the former authors demonstrated the occurrence of a secondary activation in about 50% of the skin reactions resulting from intradermal inoculation of certain strains of *Streptococcus viridans*. This secondary reaction occurred about 8 or 9 days after inoculation when the lesions had become sterile. It was considered to be allergic in type and was proved to be more similar to the tuberculin reaction than to the Arthus phenomenon. Later, these same authors were able to show that animals who showed secondary skin reactions had developed a general state of hypersensitiveness or allergy and that the eyes also had become allergic to the particular strain of streptococcus injected. Normal rabbits showed only a slight transient reaction if the cornea was scarified and a drop of bacterial sediment was rubbed into the cornea. In animals who had had a secondary skin reaction, similar inoculation of the cornea produced definite keratitis which persisted for from 2 to 15 days. This hypersensitive state could not be produced by primary intravenous injection of the streptococci. The establishment of an inflammatory focus seemed to be necessary to the production of the general and ocular allergy. The most marked reactions were obtained from foci in the skin, joints, and paranasal sinuses, but reactions were obtained also following injections into the subcutaneous tissues, muscles, peritoneal cavity, testicles, and vaginal mucosa. They demonstrated further that, ordinarily, streptococci of the viridans type injected intravenously disappear quickly from the blood stream without producing gross lesions. In some instances, however, especially when large doses are employed, the animals develop endocarditis or arthritis. These animals show hypersensitive rather than immune reactions on skin-test inoculations. Presumably, this holds true also for streptococci which have localized in the nasal tissues.

In 1931, the Seegals published their observations on ocular allergy. They found that: 1, rabbit eyes sensitized with guinea pigs' red blood cells or fresh egg white responded with an inflammatory reaction following the intravenous injection of the homologous but not of the heterologous antigen; 2, injection into the anterior chamber of 0.2 cc. of a multiple antigen containing ten separate ingredients is sufficient to ,

produce ocular hypersensitivity so that intravenous injection of 1 cc. of any one of the antigens will produce an inflammatory reaction in the sensitized eye. This hypersensitivity will persist for at least 8 months; 3, repeated daily intravenous injections of a single antigen fail usually to produce a reaction after the first few days. Injections of different antigens on succeeding days produce a continued sterile inflammatory process. Animals may develop minimal eye reactions following repeated intravenous injections of the same antigen if sufficient time is allowed to elapse between injections; and 4, unless massive doses of antigen are used to desensitize, permanent desensitization of the eye has not occurred in animals which have been followed for at least 8 months. The reaction is specific to the antigen originally used to sensitize the eye and does not depend on simple trauma to the eye. The Seegals demonstrated that a sterile inflammation may develop in the actively sensitized rabbit eye following the introduction of homologous antigen into the gastro-intestinal tract. Such reactions developed in 29% of 37 rabbits.

In 1932, A. L. Brown^{3a,4} stated: "The ability of a toxin to sensitize local ocular tissues is significant in that it may be possible for a focus of organisms to eliminate some absorbable substance into the circulation and so sensitize the uveal tract that the recurrences of uveitis might represent periods of hypersensitiveness and the remissions periods of desensitization." He confirmed the findings of the Seegals that intra-ocular sensitization could be produced routinely only by the intra-ocular presence of the sensitizing medium. He found that guinea pig red blood cells or egg white produced typical ocular anaphylaxis when injected intravenously, provided the anterior chamber had been injected with the same material 10 days previously. The reaction did not occur if the first injection had been made under the conjunctiva and developed in lesser degree if the injection was made into the vitreous chamber.

Brown tested the ability of bacterial products to produce similar ocular allergy. He isolated a hemolytic streptococcus from an infected tooth root of a man with uveitis and injected a dilute suspension in sterile water into the anterior chambers of rabbits. Iritis developed within 14 to 48 hours and subsided in 5 to 6 days. On the tenth day, he injected 2 cc. of a heavy suspension of the same organism into an ear vein. Acute iritis developed in 8 to 10 hours but subsided in 24 to 30 hours. He obtained similar results with the use of toxin from the streptococcus of scarlet fever.

In 1934, A. L. Brown^{3b,c} reported on a series of experiments designed to test the relative importance or frequency of direct metastatic focal infection and of ocular allergy in the production of iritis and uveitis. Using a strain of streptococcus known to produce iritis when injected into the earotid artery, foci of infection were implanted in parts remote from the eye. Ocular inflammation developed in one of 80 animals. When the eye had been sensitized previously by a toxic filtrate of the organism injected into the anterior chamber, the remote foci activated the eye in 25 of 30 rabbits. A similar strain of streptococcus was injected intravenously into 25 rabbits. Iritis developed in one of the 25. When the eye had been sensitized previously, iritis developed in 98 of 100 rabbits in which the streptococci were injected intravenously. In 1934, Traut obtained positive blood cultures in 5 patients with acute

iritis. However, Brown could get positive blood cultures in only 2 of 81 cases with active intraocular inflammation. One of these was in a patient with a septic abortion and the other in a patient with a blood-stream infection resulting from pyelitis. Brown cultured 37 specimens of aqueous from 27 cases of recurrent iridocyclitis, 5 sections of iris obtained by iridectomy, and the uveal tracts of 5 enucleated eyes. He was unable to recover any streptococci.

As a result of his studies, A. L. Brown concluded that the uveal inflammation produced by local bacterial sensitization is in most respects comparable to recurrent human uveal inflammation and that recurrent uveitis is probably due to the fact that the uveal tract is sensitized and activated repeatedly by a specific antigen.

To determine the efficacy of foreign protein therapy in the treatment of iritis and uveitis, A. L. Brown, 3d, studied the bactericidal properties of the aqueous and vitreous and the "interference" effect of parenteral administration of proteins on sensitization of the uveal tract. Cronstedt had found that the vitreous had essentially no bactericidal properties. Brown found that the aqueous was no more effective than the vitreous in inhibiting the growth of organisms. A suspension of organisms injected into the carotid artery usually produces panophthalmitis in the eye of the same side, if the organism is sufficiently virulent. He was able to protect the eye against inflammation by the preliminary introduction of blood serum or preferably whole blood into the vitreous chamber. He also demonstrated that multiple ocular sensitization depends on the intraocular introduction of the antigens at the same time in practically equal quantities. Larger quantities of one protein, especially if administered first, clearly inhibit the sensitizing action of smaller quantities of another protein. In an animal generally immunized to typhoid vaccine to a relatively high serum titer, the eye could be sensitized by an average dose of bacterial antigen when the aqueous titer was 1 to 2, or even 1 to 18. With an aqueous titer of above 1 to 36, sensitization was not effected. If the typhoid antibodies were in the aqueous in a concentration of at least 1 to 78 before the introduction of the bacterial antigen, the ocular reaction failed to occur.

According to A. L. Brown, the blood titer in rabbits after typhoid immunization is 1 to 4000+. The aqueous titer is only 1 to 2. After puncture of the anterior chamber, the second aqueous has a titer of 1 to 18. After a second puncture, the titer of the third aqueous is 1 to 162. If three strips of surgical 10-day catgut, 10 mm. in length, soaked in typhoid vaccine were buried under the conjunctiva, the titer of the aqueous rose to 1 to 120 in 24 hours. After 8 days, the aqueous titer was 1 to 162. Brown has suggested, therefore, the advisability of puncturing the anterior chambers after the intravenous administration of typhoid vaccine in patients with resistant iritis or uveitis. The use of subconjunctival strips of catgut might also be permissible in certain cases.

MacLean¹¹ gave probable further support to the allergic theory of recurrent uveitis when he reported, in 1936, the production of iridocyclitis in both eyes of rabbits after local sensitization of only one eye. The inflammation developed less frequently in the untraumatized eye and was less pronounced when it occurred. Dutch rabbits were sen-

sitized by intravenous injection to a strain of *Streptococcus viridans* isolated from a patient with rheumatic fever. Scarification of the corneas and inoculation of a concentrated live broth culture of the streptococci proved that the corneas participated in the general sensitivity. Four months later, after the ocular reaction had entirely subsided, live broth cultures of the streptococci were injected intravenously. Thirty minutes after the injection, blood cultures were positive but aqueous cultures were negative. Within 24 to 48 hours, both eyes of all but one of the sensitized rabbits showed marked intraocular reactions. The keratitis was reactivated in all of the sensitized animals that had had the ophthalmic test previously. Reactions were obtained in 4 of 8 rabbits, even after the fourth intravenous injection. An agar focus was established under the skin of the back in the same rabbits one week later. An intraocular reaction developed in 2 of the rabbits.

Objections can be raised to the acceptance of the allergic mechanism demonstrated experimentally to produce iritis in animals as the mechanism of recurrent iritis and uveitis in man. The most potent objections are similar to those advanced against the theory of elective localization of bacteria. The intraocular inflammations are not identical, either clinically or histologically, with those seen in humans. The inflammations are more transitory and do not run the protracted course of many cases of human iritis and most cases of uveitis. Recurrence of the inflammation can be produced more readily by sensitization methods than by direct intravenous injections of specific bacteria. But the recurrences tend to be increasingly milder and more transient rather than more severe and resistant as they are in many clinical cases.

Alan Woods,¹⁶ in the section on "Immunology" in Berens' "The Eye and Its Diseases," states: "Kolmer⁹ and others have suggested that many inflammatory diseases of the eye—keratitis, iritis, and uveitis—which clinically appear to be related to foci of infection, in many instances may be due to allergy and not to bacterial metastasis. The grounds advanced for such reasoning are the usual inability to culture bacteria from the inflamed eye or its humors, and the flare-ups in the inflammatory ocular picture which often follow the administration of a vaccine obtained from the primary focus of infection." After discussing the necessity of proving 1, that patients with uveitis and other forms of ocular disease have a higher degree of sensitivity than normal individuals to bacteria isolated from foci of infection, and 2, that clinical improvement follows desensitization with the bacterial products, Woods concludes: "It is therefore evident that while experimental evidence indicates that certain eye lesions from a focus of infection may be due to an allergic mechanism rather than to bacterial metastasis, clinical proof of such an allergic mechanism is lacking, and must of necessity be difficult to produce." It seems possible that the "elective localizing" character of the streptococci concerned in these diseases may account at least for the local ocular hypersensitiveness exhibited by patients with recurrent uveitis. Recently, Rosenow has noted specific skin reactions in humans to hyperimmune sera produced in horses by repeated injections of specific strains of streptococci. This finding suggests that individuals suffering from recurrent iridocyclitis or uveitis may be hypersensitive or allergic to the products of a strep-

toëoccus with specific affinity for the uveal tract. The attacks of uveitis may occur then only at those times when the streptococci in the focus of infection develop this specific affinity.

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REFERENCES.

- (1.) Andrews, C. H., Derick, C. L., and Swift, H. F.: *J. Exp. Med.*, 44, 35, 1926.
- (2.) Benedict, W. L.: *Arch. Ophthal.*, 50, 560, 1921. (3.) Brown, A. L.: (a) *Am. J. Ophthal.*, 15, 19, 1932; (b) *Trans. Sect. Ophthal. Am. Med. Assn.*, p. 111, 1934; (c) *Arch. Ophthal.*, 12, 730, 1934; (d) *Tr. Am. Ophthal. Soc.*, 33, 435, 1935. (4.) Brown, A. L., and Dummer, C.: *J. Exp. Med.*, 13, 238, 1932. (5.) Derick, C. L., and Andrews, C. H.: *Ibid.*, 44, 55, 1926. (6.) Derick, C. L., and Swift, H. F.: *Ibid.*, 49, 615, 1929. (7.) Haden, R. L.: *Arch. Int. Med.*, 32, 829, 1923. (8.) Irons, E. E., Brown, E. V. L., and Nadler, W. H.: *J. Infect. Dis.*, 18, 315, 1916. (9.) Kolmer, J. A.: *Am. J. Ophthal.*, 14, 217, 1931. (10.) Lewis, F. P.: *J. Am. Med. Assn.*, 73, 1132, 1919. (11.) MacLean, A. L.: *Trans. Am. Ophthal. Soc.*, 34, 324, 1936. (12.) Rosenow, E. C.: *J. Infect. Dis.*, 17, 403, 1915. (a) *Trans. Am. Acad. Ophthal. and Otolaryngol.*, 32, 41, 1927. (13.) Rosenow, E. C., and Nickel, A. C.: *Am. J. Ophthal.*, 15, 1, 1932. (14.) Seegal, D., and Seegal, B. C.: (a) *J. Exp. Med.*, 54, 249, 1931; (b) *Ibid.*: p. 265. (15.) Swift, H. F., and Derick, C. L.: *Ibid.*, 49, 883, 1929. (16.) Woods, A. C.: *Immunology. The Eye and Its Diseases* (edited by Conrad Berens), W. B. Saunders & Co., Philadelphia, p. 1174, 1936.

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ORIGINAL ARTICLES.

CONGO RED IN THE TREATMENT OF PERNICIOUS ANEMIA
AND SPRUE.

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IN 1933, Massa and Zolezzi,^{6a} at the University of Parma Medical Clinic, announced the successful treatment of 2 cases of pernicious anemia with intravenously administered Congo red. A year later they reported favorable results in a larger series of cases.^{6b} In 1935, Mermod and Doek⁵ apparently confirmed the observations of the Italian authors. Since Congo red is a synthetic colloidal dye with a known chemical formula, it seemed most important to test further the use of this compound in the treatment of pernicious anemia.

Massa and Zolezzi employed a 0.5% solution of Congo red (Grübler) made up in 0.5% saline solution. This solution was warmed almost to boiling, allowed to stand 24 hours, and then filtered through paper. The filtrate was placed in ampules and sterilized by autoclaving for 10 minutes at $\frac{3}{4}$ to 1 atmosphere. Injections of 20 cc. of this solution were given every 1 to 2 days for 5 to 6 days followed by a rest period of several days. Of fifteen cases treated with Congo red, as far as can be ascertained from the brief case reports, the majority satisfied the usual criteria for the diagnosis of pernicious anemia, *i. e.*, a macrocytic hyperehromic anemia, hyperbilirubinemia, and achylia gastrica. Of the 15 cases, 3 may be dismissed at once as they were given a short course of liver therapy prior to the injections of Congo red. The authors felt that the continued improvement on Congo red pointed to a specific therapeutic effect of the dye; however, as it is well

established that small amounts of liver may produce complete and prolonged remissions in pernicious anemia, it would be impossible to evaluate the efficacy of Congo red in these 3 cases. Of the remaining 12 treated with Congo red alone, 9 had complete blood remissions, whereas 3 failed to respond at all. After receiving a fair trial of the dye, these latter 3 were treated energetically with liver extract to which they responded favorably. Reticulocytes were followed in 5 of the 9 cases which showed remissions on Congo red alone; in these 5 cases reticulocyte peaks of 10 to 25% occurred after the eighth or ninth injection. All of the patients treated successfully with Congo red remained clinically well for the several months of observation following treatment. In an attempt to explain the therapeutic effect of Congo red, Massa and Zolezzi suggested that the dye prevented hemolysis by blocking the reticulo-endothelial cells.

Mermod and Dock reported that they had confirmed the results of Massa and Zolezzi by successfully treating 2 cases of mild pernicious anemia with intravenous Congo red. These authors employed a 1.5% solution of the dye in 6% glucose solution. One patient received 60 cc. of this solution in 5 days, the other 90 cc. in 10 days. Both patients showed a rise in reticulocytes and a fall in serum bilirubin. As soon as the reticulocyte peak was passed, the treatment was changed to liver extract. It is therefore open to question whether complete blood remissions would have followed the reticulocyte crises if Congo red therapy had been continued. Mermod and Dock point to the fact that Congo red is notably effective in neutralizing a variety of toxins and suggest that "in pernicious anemia the dye assists in the detoxification of substances, probably enterogenous in origin, which are hemolytic."

A brief abstract of the results obtained in the treatment of pernicious anemia with Congo red at our clinic has recently appeared.¹ It is the purpose of the present report to give these results in more detail with some additional data.

Because of the difficulty in obtaining suitable cases of pernicious anemia in relapse, the problem was at first attacked from a somewhat different angle. Proven cases of pernicious anemia, which were in a remission as the result of liver extract therapy, were selected from the outpatient clinic. Weekly intravenous injections of Congo red (Grübler) solution were substituted for intramuscular liver extract injections.* A 0.5% solution of the dye in 0.5% saline, prepared exactly according to the method of Massa and Zolezzi, was employed in all cases. Only patients without evidence of combined system disease were selected. Six such patients were treated with Congo red for periods varying from 9 weeks to 6 months. The blood changes

* Liver Extract Lilly N.N.R. was used throughout this study. The solution for intramuscular injection was made up so that 1 cc. of solution contained the amount of extract derived from 5 gm. of whole liver.

are illustrated by Charts I to VI and summarized in Table 1. It is evident that 5 of the 6 patients in this group evinced a marked tendency to relapse as shown by falling red count and hemoglobin as well as by rising mean corpuscular volume and color index. In 4 of the cases distinct symptoms of relapsing pernicious anemia appeared concomitant with the characteristic blood changes. The symptoms disappeared rapidly and the blood levels soon returned to normal when intramuscular liver extract therapy was resumed. These relapses during Congo red therapy are the more significant in that no attempt was made to control the diets of these patients, who had been previously trained to eat plenty of meat and other foods rich in Castle's extrinsic factor. As it is not unusual for pernicious anemia patients to maintain remissions for 6 months or longer without any specific therapy, it would certainly appear that weekly injections of Congo red completely fail to increase their chances of maintaining a remission. The criticism may be raised that these patients were not given sufficient Congo red and that larger or more frequent injections might have succeeded where the selected dosage failed. This is a valid objection, and it would not be safe to conclude from this experiment alone that Congo red is ineffective in pernicious anemia. The conclusion is justified, however, that weekly injections of Congo red did not furnish a practical substitute for liver extract in this group of patients, all of whom could be maintained in a complete remission by a single injection of liver extract once every 2 to 3 weeks.

TABLE 1.—BLOOD CHANGES DURING CONGO RED THERAPY.

Case No.	Patient.	Duration of R (wks.).	Total Congo red (cc.).	R. B. C. (millions).		Hb (%).		M.C.V. (μ^3).		C.I.	
				Before.	After.	Before.	After.	Before.	After.	Before.	After.
1	C. T.	9	160	4.09	2.90	90	77	95	104	1.10	1.32
2	C. M.	15	260	4.36	2.72	104	78	103	115	1.19	1.44
3	J. B.	18	360	4.36	2.66	105	74	104	112	1.20	1.39
4	I. F.	24	480	4.47	3.17	95	87	93	116	1.06	1.37
5	F. A.	25	500	4.97	1.99	101	63	92	132	1.02	1.58
6	M. A.	25	500	4.01	3.94	88	93	102	107	1.10	1.18
Aver.				4.38	2.90	97	79	98	114	1.11	1.38
Change				-1.48		-18		+16		+0.27	

More recently the opportunity arose to study the effect of Congo red in 2 cases of pernicious anemia in relapse. These patients were admitted to the ward and placed upon a diet low in Castle's extrinsic factor for some time before Congo red therapy was instituted.

This procedure eliminated any possibility of a dietary effect and at the same time established a reticulocyte baseline. In the first patient (Case 7, Chart VII), daily intravenous injections of Congo red over a 2-week period failed to produce either subjective improvement or an increase in the reticulocytes, yet a subsequent small dose of liver extract gave rise to a satisfactory reticulocyte response at the expected time with the associated subjective improvement. The second patient (Case 3, Chart III), 1 of the cases which had relapsed while receiving weekly injections of Congo red, was admitted to the ward in order to see whether intensive Congo red therapy would succeed where weekly injections had failed. This patient, given daily injections of Congo red over a 3-week period, showed a minimal reticulocyte rise to 4% on the ninth day. Since there was no subjective improvement or change in the blood levels during the 3-week period this slight reticulocytosis was most likely a non-specific response. Thus in 2 cases of pernicious anemia in relapse, daily intravenous injections of Congo red completely failed to produce clinical or hematologic improvement.

Two cases of sprue were treated with Congo red in order to determine whether the dye might exert a therapeutic effect in this disease so similar to pernicious anemia in its response to liver extract. The first patient (Case 8) had been maintained free of symptoms over a long period on a sprue diet supplemented with a single injection of liver extract every 2 to 3 weeks. The diet was kept constant and weekly injections of 20 cc. of the Congo red solution were substituted for the liver extract régime. Within 4 weeks of the last liver extract injection the patient developed nausea and diarrhea, which became so severe that after 6 weeks the dye was discontinued and liver-extract therapy renewed with almost immediate alleviation of symptoms. The second patient (Case 9) was a known sprue patient suffering from diarrhea as a result of lapsing liver extract treatment for several weeks. This patient was brought into the hospital; in spite of daily injections of 20 cc. of the Congo red solution for 1 week, the diarrhea persisted and an aphthous stomatitis developed. Both the diarrhea and the stomatitis cleared up rapidly when liver extract injections were resumed.

Case Reports. CASE 1.—C. T., female aged 42 (Chart I). Onset of fatigue, yellow pallor, and sore tongue in 1929. Remission on liver extract shortly after onset. Relapsed when liver was discontinued. First came to clinic May, 1933.

Physical Examination. Lemon-yellow pallor. Marginal papillary atrophy of tongue. Palpable spleen. *Blood:* R.B.C. 1,800,000; Hgb. 43%; C.I. 1.19. *Gastric Analysis:* No free HCl, even after histamine. *Course:* Patient was treated with intravenous liver extract at first; later 10 cc. intramuscular liver extract every 2 weeks. Blood levels rose to normal and remained there. On September 30, 1935, R.B.C. 4,090,000; Hgb. 90%; M.C.V. 95; C.I. 1.10. On this date therapy changed to 20 cc. of Congo red solution once a week. At the end of 9 weeks R.B.C. had dropped

to 2,900,000 and Hgb. to 77%; patient weak and tired, tongue very sore. Congo red discontinued and liver extract resumed with rapid symptomatic and hematologic improvement.

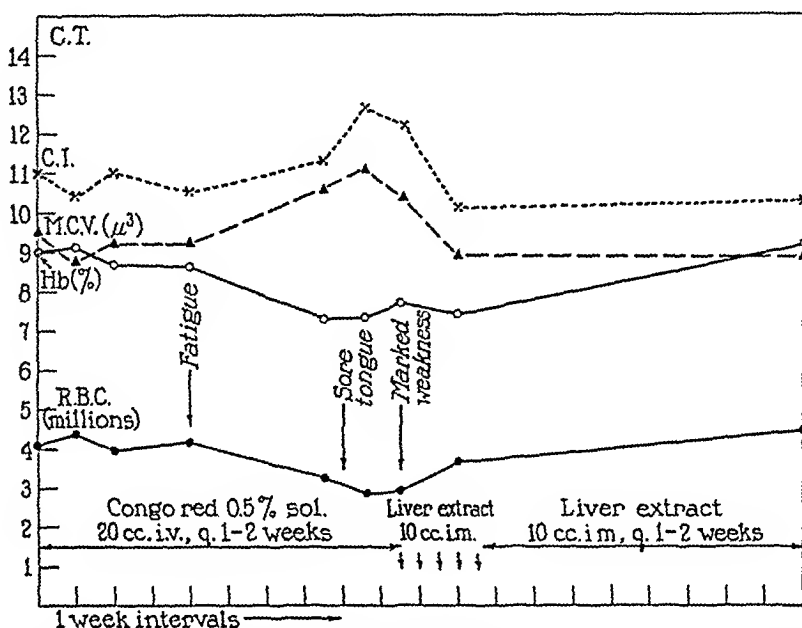


CHART I.—Case 1. Pernicious anemia. Rapid relapse during 9-week period of Congo red therapy.

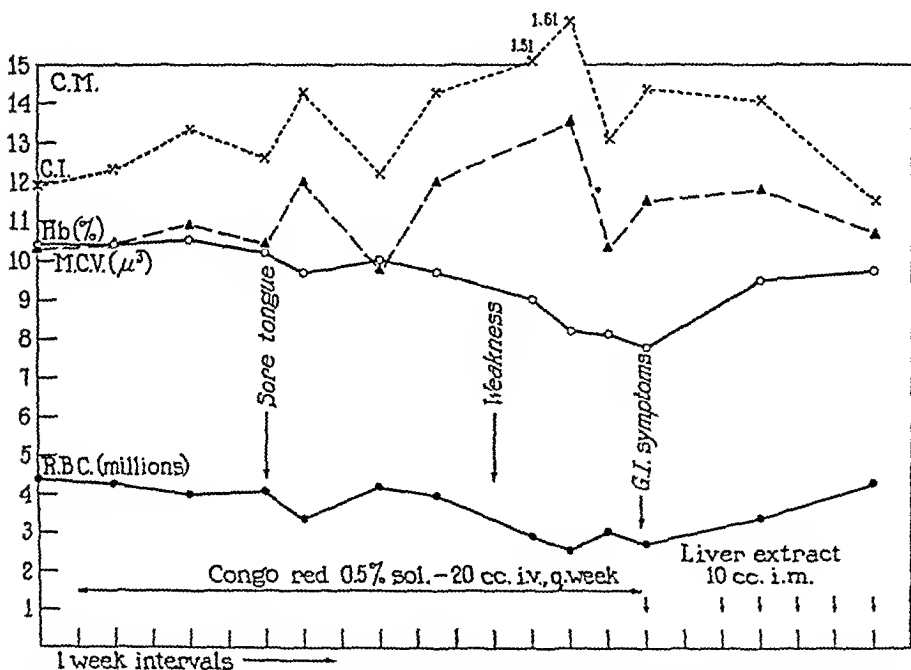


CHART II.—Case 2. Pernicious anemia. Relapse during 15-week period of Congo red therapy.

CASE 2.—C. M., male aged 60 (Chart II). In 1929 onset of fatigue, anorexia, sore tongue, paresthesias in legs, and anemia. Temporary

improvement on oral liver; incomplete response to small doses of parenteral liver extract. February, 1933, admission to the hospital. *Physical examination:* Lemon-yellow pallor, marked papillary atrophy of tongue. Palpable spleen. Slightly diminished vibratory sense in legs. *Blood:* R.B.C. 960,000; Hgb. 24%; C.I. 1.26; W.B.C. 2250. *Gastric analysis:* No free HCl even after histamine. *Bone marrow:* Typical of pernicious anemia. *Course:* Remission on intravenous liver extract. Maintained in good health with blood at normal levels on 10 cc. of liver extract intramuscularly every 2 weeks. On October 3, 1935, R.B.C. 4,360,000; Hgb. 104%; M.C.V. 103; C.I. 1.19. Therapy changed to 20 cc. Congo red solution intravenously once a week. Glossitis and weakness developed. After 15 weeks R.B.C. had fallen to 2,720,000 and Hgb. to 78%. Congo red discontinued and intramuscular liver extract resumed with rapid remission.

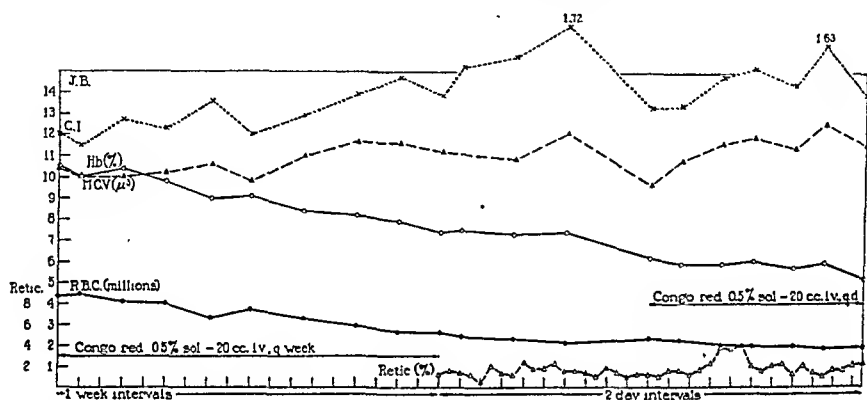


CHART III.—Case 3. Pernicious anemia. Relapse during 4-month period of weekly injections of Congo red. Failure to improve on daily injections of Congo red over 3-week period.

CASE 3.—J. B., male aged 40 (Chart III). History of onset of weakness, fatigue, anorexia, sore tongue, and yellow pallor in 1928. Diagnosis of pernicious anemia was made and patient improved on liver therapy. Treatment was irregular and he suffered several relapses. First seen at this hospital June, 1935, with R.B.C. 3,500,000 and Hgb. 94%. Liver extract 10 cc. given intramuscularly every 2 weeks; on this régime he felt very well; R.B.C. 4,360,000 and Hgb. 105%, with M.C.V. 104 and C.I. 1.20 in October, 1935, at which time therapy was changed to 20 cc. of Congo red solution intravenously once a week. This therapy was kept up for 18 weeks; during this period R.B.C. and Hgb. fell; M.C.V. and C.I. rose. He complained of increasing fatigue, exertional dyspnea, and finally soreness of tongue. He was then admitted to the hospital and placed on a meat-free diet. *Physical examination:* Moderate pallor. Redness of tongue. Slight diminution of vibratory sense in feet. *Blood:* R.B.C. 2,660,000; Hgb. 74%; M.C.V. 112; C.I. 1.39; Icteric Index 8; W.B.C. 6650. *Gastric analysis:* No free HCl even after histamine. *Course:* After 3 weeks on meat-free diet R.B.C. 2,000,000 and Hgb. 60%; icteric index 15. Daily intravenous injections of 20 cc. of Congo red solution were then given for 3 weeks. On 9th day reticulocytes had reached a low peak of 4% and then fell to original level below 2%. There was a slight fall in R.B.C. and Hgb. during the 3-week period and serum bilirubin remained elevated; the patient experienced no subjective improvement. Intramuscular liver extract therapy was subsequently renewed and blood levels rapidly returned to normal.

CASE 4.—I. F., female aged 39 (Chart IV). In 1934 onset of weakness, dizziness, pallor, anorexia, loss of weight. R.B.C. down to 1,000,000. Remission on liver extract but relapse with sore tongue and paresthesias when therapy was discontinued. Admission to the hospital July, 1935. *Physical examination:* Pallor. Slight icterus. Moderate papillary atrophy. Spleen just palpable. No neurologic disturbance. *Blood:* R.B.C. 2,080,000; Hgb. 58%; M.C.V. 121; C.I. 1.45; W.B.C. 5600. *Course:* Blood levels rose to normal on intramuscular liver extract and remission was maintained with a single injection of 10 cc. liver extract every 2 weeks. In September, 1935, R.B.C. 4,470,000; Hgb. 95%; M.C.V. 93; C.I. 1.06. Therapy changed to 20 cc. of Congo red solution once a week. After 24 weeks R.B.C. 3,170,000 and Hgb. 87%; the patient complained of weakness and sore tongue. Liver extract resumed with rapid improvement and 6 months later she is quite well with normal blood levels on a single injection of liver extract every 2 weeks.

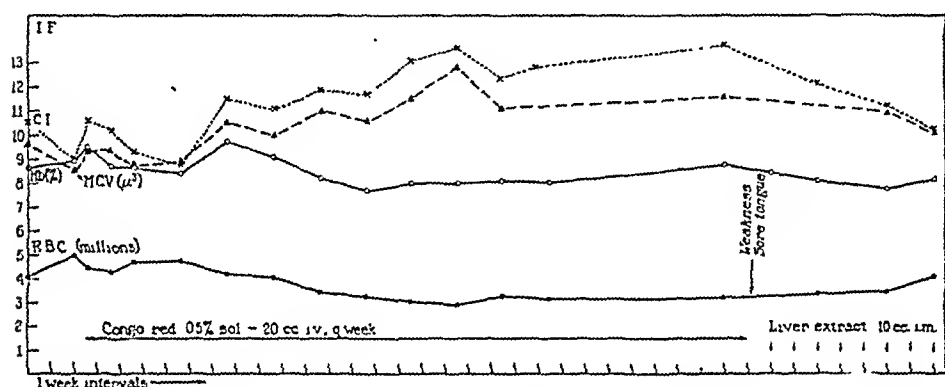


CHART IV.—Case 4. Pernicious anemia. Gradual relapse during 5½-month period of Congo red therapy.

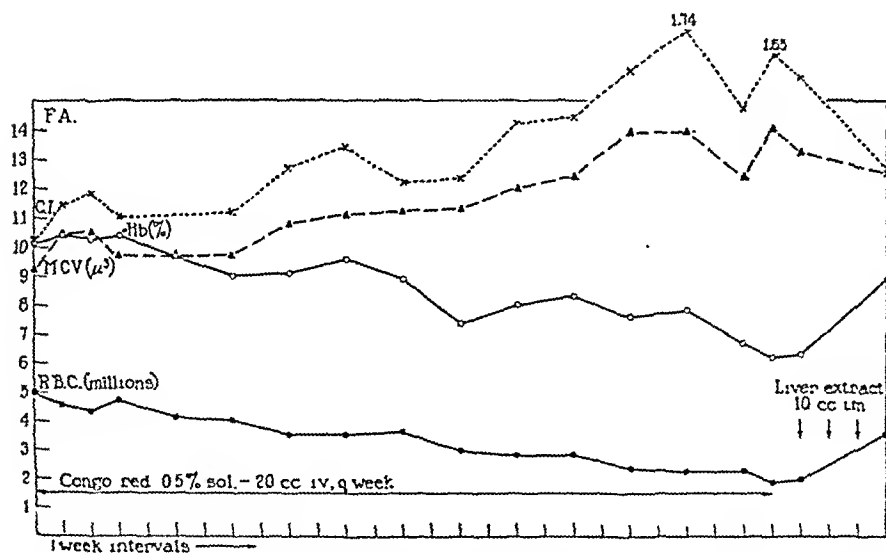


CHART V.—Case 5. Pernicious anemia. Gradual relapse during 6-month period of Congo red therapy.

CASE 5.—F. A., male aged 59 (Chart V). Onset of weakness, sore tongue, and yellow pallor in 1929. Hgb. was 35%. On oral liver extract marked

symptomatic improvement and Hgb. rose to 95%. Five years later, relapse because of inadequate therapy. April, 1935, admission to the hospital. *Physical examination:* Emaciation. Lemon-yellow pallor. Marginal papillary atrophy of tongue. Neurologic examination normal. *Blood:* R.B.C. 1,220,000; Hgb. 33%; C.I. 1.32; W.B.C. 3150; plasma bilirubin 2.65 mg.%; *Gastric analysis:* No free HCl even after histamine. *Course:* Reticulocyte peak of 25%, 5 days after intramuscular liver extract; R.B.C. and Hgb. returned to normal and patient was maintained in good health on 10 cc. of liver extract intramuscularly every 2 weeks. On September 23, 1935, R.B.C. 4,970,000; Hgb. 101%; M.C.V. 92; C.I. 1.02. Therapy changed to 20 cc. of Congo red solution once a week. At the end of 25 weeks R.B.C. 1,990,000 and Hgb. 63% with M.C.V. 132 and C.I. 1.58; moderate weakness his only complaint. Intramuscular liver-extract therapy resumed with rapid return of blood levels to normal.

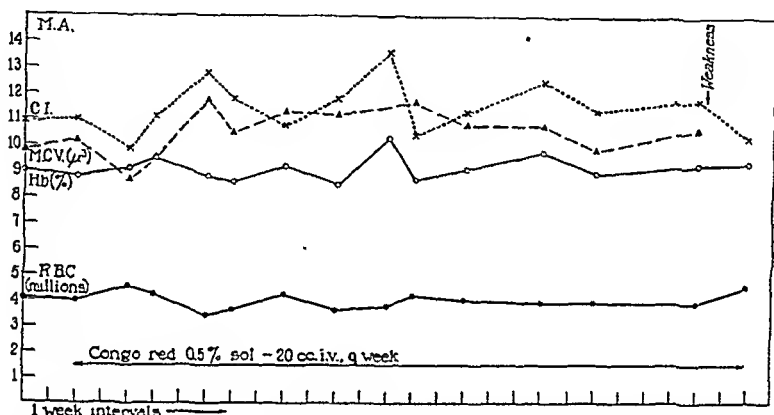


CHART VI.—Case 6. Pernicious anemia. Course of blood count during 6-month period of Congo red therapy. In contrast with Cases 1 to 5 this patient showed no essential change in blood picture.

CASE 6.—M. A., female aged 37 (Chart VI). Three-year history of weakness, pallor, sore tongue and anemia. Temporary remission on liver extract. Discontinued therapy and admitted in relapse in February, 1935. *Physical examination:* Lemon-yellow pallor. Extreme papillary atrophy of tongue. Palpable spleen. Sluggish tendon reflexes. *Blood:* R.B.C. 1,115,000; Hgb. 35%; M.C.V. 134; C.I. 1.51; W.B.C. 3500. *Course:* Reticulocytes rose to 21% following intramuscular liver extract; R.B.C. and Hgb. returned to normal. Complete remission maintained with 10 cc. liver extract intramuscularly every 2 weeks. On October 10, 1936, R.B.C. 4,010,000; Hgb. 88%; M.C.V. 102; and C.I. 1.10. Therapy changed to 20 cc. Congo red solution intravenously once a week. After 25 weeks, no definite symptoms of relapse and no appreciable change in blood levels. Therapy changed back to liver extract.

CASE 7.—F. G., Italian male aged 54 (Chart VII). Admitted to hospital September 3, 1935. History of weakness, loss of weight, and dizziness for 2½ years. Temporary improvement on oral liver. Symptoms recurred when he stopped liver therapy. Developed anorexia, abdominal discomfort, and paresthesias in extremities. *Physical examination:* Moderate pallor. Marginal papillary atrophy of tongue. Slight diminution of vibratory sense in feet. *Blood:* R.B.C. 2,490,000; Hgb. 76%; M.C.V. 133; C.I. 1.52; W.B.C. 4400. *Gastric analysis:* No free HCl, even after histamine.

Course: Patient was placed upon meat-free diet for several weeks; weakness and indigestion increased; tongue became sore. Reticulocytes stabilized below 2%. Congo red solution (20 cc.) given daily for 6 days, followed by 40 cc. daily for 5 days. No rise in reticulocytes in 2 weeks. Patient then given single injection of 5 cc. liver extract (the amount derived from 25 gm. of whole liver) intramuscularly. Reticulocytes reached peak of 9% on 6th day with marked subjective improvement. Complete blood remission followed further liver-extract therapy, and for the past year the patient has remained symptom-free with normal blood levels on 10 cc. of liver extract intramuscularly every 2 weeks.

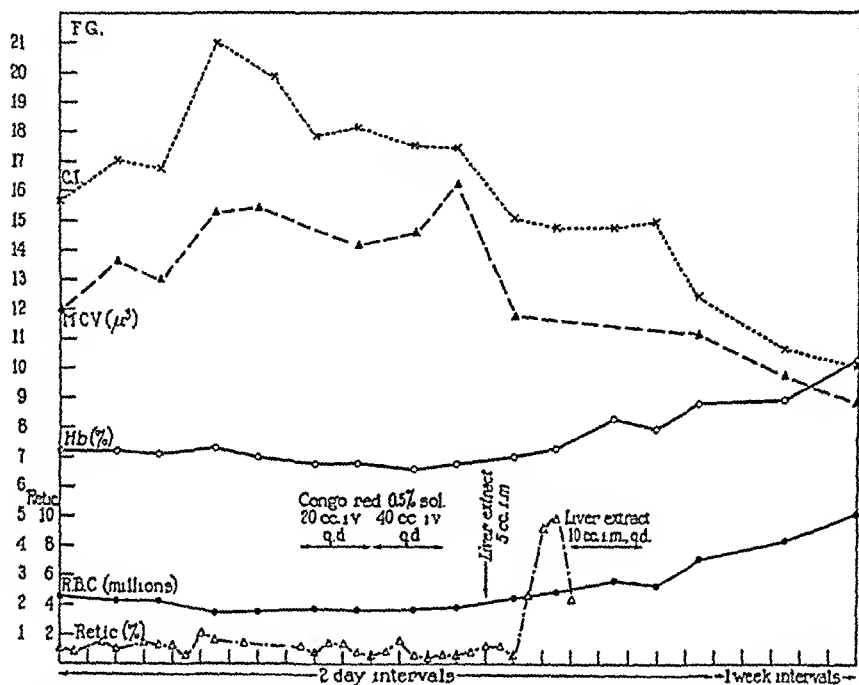


CHART VII.—Case 7. Pernicious anemia in relapse. Failure of daily injections of Congo red to modify the blood picture. Subsequent response to liver extract.

CASE 8.—R. D., female aged 50, had lived in China 21 years. During the last 7 years of her stay she suffered from repeated attacks of diarrhea associated with soreness of tongue and mouth. Temporary relief of symptoms on diet of liver and sour milk. Later recurrence; oral liver extract failed to give relief. Severe anemia developed. Patient admitted to the hospital in 1931. *Physical examination:* Marked emaciation and pallor. Papillary atrophy of tongue. Palpable spleen. *Blood:* R.B.C. 820,000; Hgb. 22%; M.C.V. 131; C.I. 1.34; icteric index 20. *Gastric analysis:* Free HCl present only after histamine injection. *Course:* With intensive parenteral liver-extract therapy, diarrhea ceased, soreness of tongue cleared, and blood levels returned to normal. For the next 4 years she remained symptom-free on sprue diet augmented by an intramuscular injection of 10 cc. of liver extract every 2 to 3 weeks. If she tried to increase the interval between liver-extract injections to 4 weeks or longer, she invariably developed gastro-intestinal symptoms which were in turn rapidly alleviated by a single injection of liver extract. In December, 1935, therapy was changed from an intramuscular injection of liver extract once every 3 weeks to weekly intravenous injections of 20 cc. of Congo red solution. The diet

was kept constant. Within 4 weeks of the last liver extract injection nausea and diarrhea set in. These symptoms increased in severity; at the end of 6 weeks the Congo red injections were abandoned and an injection of 10 cc. of liver extract was given intramuscularly. Within 36 hours of this liver extract injection, all symptoms had vanished.

CASE 9.—B.M., female aged 37, had resided for 12 years in Cuba. For 7 years recurrent attacks of diarrhea, nausea, vomiting, and abdominal cramps. Two years after onset of diarrhea sore mouth and anemia developed. Temporary improvement on sprue diet and oral liver extract; later symptoms recurred and failed to respond to oral therapy. Admission to hospital February, 1935. *Physical examination:* Marked pallor. Papillary atrophy of tongue with aphthous ulceration of buccal mucosa. Abdominal distention. *Blood:* R.B.C. 2,000,000; Hgb. 66%; M.C.V. 135; C.I. 1.65. *Gastric analysis:* Free HCl present after alcohol test meal. *Course:* On intramuscular and intravenous liver extract symptoms ceased and blood levels returned to normal. After discharge from the hospital patient was symptom-free for nearly a year on a sprue diet with a single intramuscular injection of 10 cc. of liver extract every 2 weeks. She then lapsed treatment and soon developed severe diarrhea and soreness of the tongue. She was readmitted to the hospital and given daily intravenous injections of 20 cc. of Congo red solution for 1 week. During this period diarrhea continued and a crop of aphthous ulcers appeared in the mouth. She was then given daily intramuscular injections of liver extract for 5 days. Soreness of the tongue disappeared after the first injection and the aphthous ulcers healed rapidly. Diarrhea ceased after the third injection of liver extract. The patient has since been maintained in excellent health on injections of liver extract once or twice a week.

Comment. There is obviously a marked discrepancy between the results that we obtained with Congo red and those reported by Massa and Zolezzi. Recently Lendvai,⁴ in Budapest, has published a series of 12 cases of pernicious anemia treated with intravenous Congo red. All of his patients were in severe relapse with erythrocyte counts varying from 800,000 to 2,200,000 red blood cells per c.mm. and hemoglobin levels of 28 to 64%. They received from 8 to 20 injections of 10 cc. of a 0.5% solution of Congo red over periods of 10 days to 4 weeks. Reticuloeytes were followed in all cases and 4 cases showed slight reticuloeyte rises of 4 to 8%; there was no increase in the reticuloeytes in the other 6 cases. In no case did the red blood cell count or the hemoglobin rise above the pre-treatment levels. Subsequent treatment with liver effected a complete blood remission in every case. Bone marrow was aspirated at intervals during the period of observation; the smears from the marrow presented a megaloblastic picture before and after Congo red therapy but a normoblastic picture after liver-extract therapy. Lendvai regards the slight reticuloeytosis noted in certain of his cases as non-specific in type and concludes that Congo red exerts no therapeutic effect in pernicious anemia. The results of Lendvai are wholly in accord with those that we obtained in the treatment of pernicious anemia with Congo red.

Since the 2 cases of Mermod and Dock were changed to liver therapy as soon as reticuloeyte rises had been produced with Congo

red, there is no evidence that these reticulocyte crises differed in any way from the non-specific responses noted by Lendvai. Certainly there is no justification for assuming a specific therapeutic effect of Congo red in these 2 cases.

Thus the contention of Massa and Zolezzi that Congo red may bring about a complete blood remission in pernicious anemia lacks definite confirmation to date. It is quite impossible to reconcile the results reported by the Italian authors with our observations or those of Lendvai. One can only suggest: 1, that the Italian cases did not have true pernicious anemia, or 2, that they may have been individuals with "incomplete pernicious anemia." Goldhamer,³ has demonstrated the presence of a small amount of intrinsic factor in the gastric juice of patients with pernicious anemia. It is conceivable that the gastric secretion of Massa and Zolezzi's responding cases contained a fair amount of intrinsic factor; that these patients had had diets poor in extrinsic factor prior to their admission to the hospital; and that they had received far better diets in the hospital. If such were the case, they might then have been able to manufacture through the combination of extrinsic and intrinsic factors in their gastro-intestinal tracts sufficient "liver extract" to bring about blood remissions. In other words, the remissions may have been dietary in origin and not due to the Congo red.

Finally, let us assume for the moment on the basis of Massa and Zolezzi's observations that Congo red might exert some therapeutic effect in pernicious anemia. Even so, Congo red could not be compared with the active principle of liver extract, for Dakin and West² have shown that 80 mg. of their purified fraction is sufficient to bring about a maximal reticulocyte response and an increase in the blood levels of patients with pernicious anemia. If Congo red even approached this active principle in potency, then our 2 cases in relapse and the 10 cases of Lendvai, which received 400 to 2100 mg. of the dye over relatively short periods, should certainly have shown striking improvement in both the clinical and the hematologic picture.

Conclusion. Congo red is totally ineffective in the treatment of patients with pernicious anemia or sprue. The dye may occasionally produce slight non-specific reticulocyte rises in cases of pernicious anemia.

REFERENCES.

- (1.) Barker, H.: J. Clin. Invest. (Proc.), 15, 456, 1936. (2.) Dakin, H. D., and West, R.: J. Biol. Chem., 109, 489, 1935. (3.) Goldhamer, S. M.: AM. J. MED. SCI., 191, 405, 1936. (4.) Lendvai, J.: (a) Gyógyászat, 76, 145, 1936; (b) Klin. Wehnschr., 15, 1034, 1936. (5.) Mermod, C., and Dock, W.: Science, 82, 155, 1935. (6.) Massa, M., and Zolezzi, G.: (a) Gior. di clin. med., 14, 975, 1933; (b) Klin. Wehnschr., 14, 235, 1935.

EFFECT OF LEAD THERAPY ON BLOOD CELLS OF CANCER PATIENTS.

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SINCE the stimulating researches of Blair Bell on the use of lead compounds in the treatment of cancer, much experimental work has been done and varying opinions are still held regarding the efficacy of this agent. Because recently Bargen, *et al.*,² of the Mayo Clinic, reported some encouraging results with the use of lead in inoperable cancer, a similar study was undertaken at this hospital. This paper deals with the blood changes resulting from the use of colloidal lead in a group of 22 cases of advanced cancer.

Method. Colloidal lead triphosphate was prepared in this laboratory and given to patients with late cancer, according to the procedure outlined by Bargen. It was administered intravenously 2 or 3 times weekly, in doses varying from 35 to 140 mg. (10 to 40 cc.) over a period of 2 to 4 weeks. Five cases received an incomplete course of treatment, totaling 175 to 280 mg. and 17 cases were given a full course of treatment totaling 535 to 805 mg. A complete blood count, including hemoglobin (Haden-Hausser), total erythrocytes, stippled erythrocytes, total white blood cells and differential, was made before treatment, 2 to 4 times weekly during treatment, twice weekly for 4 weeks following treatment and once monthly thereafter. In 18 cases the count of stippled red blood cells as obtained by the Wright's stain was checked with Manson's borax methylene blue stain. In 1 (Case 22), stippled erythrocyte counts with Wright's stain, basophilic aggregation counts with Manson's stain, and reticulocyte counts with cresyl blue were made 2 to 4 times weekly for 9 weeks.

Effect of Lead on the Red Blood Cells. A. Findings of Previous Workers. 1. The *anemia* of lead poisoning results from the destruction of the "leaded" cells in the peripheral circulation.^{1a,15} In rabbits, after the ingestion of 1 gm. of lead, the number of circulating red cells may decrease more than 20%.^{12b} In some cancer patients reductions of approximately a million cells may occur within an hour after a single injection of lead.^{3b} Along with the destruction of circulating erythrocytes there is a compensatory regeneration. Early in lead intoxication a large number of nucleated and of reticulated red blood cells appear in the peripheral circulation.^{1a,12a} Aub^{1b} reported 6 to 16% reticulocytes in total red blood cell counts of 3,500,000.

2. *Irregularities in size⁸ and shape⁶ of the red cells occur.*

3. *Nucleated Red Blood Cells.* In shipbreakers exposed to a heavily leaded atmosphere Ferguson and Ferguson^{8a} found nucleated red cells in 56% of the blood films examined and in at least one film from every case. Of the nucleated cells 99% were normoblasts and 1% were megaloblasts. Bell, Williams and Cunningham⁴ repeatedly observed nucleated red cells as early as the fifth day following intravenous injection of lead. In Bell's work with lead therapy in cancer, nucleated red corpuscles were frequently found, and when present were invariably associated with considerable anemia and with stippling of red cells. Occasionally the nucleated red cells contained basophilic granules in their cytoplasm.

4. *Reticulocytes.* Fleckel and Tschernow⁹ approximated the degree of lead absorption in patients by determining the percentage of reticulocytes by vital staining. They regarded 0.7 to 1% reticulocytes as normal. Jones¹¹ (1933) and McCord and his co-workers¹³ (1934) advocated the use of the reticulocyte count as an index of lead absorption in place of the usual punctate basophilia count. Brookfield, and later the Fergusons, found a close correlation between the number of reticulocytes and the number of cells showing punctate basophilia.

5. *Polychromasia.* Polychromasia is always present in the immature erythrocytes of the normal bone marrow. In the peripheral blood, polychromasia is seen in the nucleated red cells and occasionally in immature non-nucleated reds, especially in anemias that are associated with active erythrocyte production. Bell's group of investigators^{3c} believed that polychromasia is a regenerative phenomenon observed constantly in lead anemia in association with punctate basophilia.

6. *Stippling.* Punctate basophilia or stippling of red blood corpuscles has long been recognized as one of the earliest and most constant phenomena in lead poisoning. Pappenheim,¹⁴ Schilling-Torgau,^{8b} Key^{12a} and Brookfield⁶ believe that polychromasia, stippling and reticulation are all due to the presence of basic staining cytoplasm of youthful origin, and are all substantially the same substance. Punctate basophilia is present classically where bone marrow is excessively active; it is regarded by some^{1,4,6,8a,10} as a degenerative phenomenon occurring in young red blood cells. It never occurs in aplastic anemia,^{8a} in which condition there is a suppression of erythrocyte formation, but it does occur chiefly in toxic anemias where the products of red-cell degeneration are retained within the body. Ferguson and Ferguson found stippling present in every slide examined during the course of their lead investigation in shipbreakers. Of the nucleated red cells seen on their slides 4% showed basophilic stippling, whereas only 0.9% of all erythrocytes showed the punctate basophilia.

B. Findings in Present Study. 1. A progressive anemia was noted after the completion of treatment in 16 of our 22 cases (Tables 1, 2). A decrease of 20% in hemoglobin and erythrocytes during or following treatment was regarded as significant, and in most cases (11 of the 16 which developed anemia) was noted 1 to 3 weeks

TABLE 1.—EFFECT OF LEAD ON HEMOGLOBIN AND ERYTHROCYTES. (ALL CASES EXCEPT 8 AND 22 DIED WITHIN A FEW DAYS AFTER THE LAST COUNT WAS TAKEN.)

Case.	Lead (mg.)	Before treatment.			After treatment (last count taken).			Weeks after treatment.
		Hb. (gm.)	R. B. C. (millions)	C. I.	Hb. (gm.)	R. B. C. (millions)	C. I.	
1	770	14.4	4.67	0.92	6.5	2.74	0.71	18
2	805	11.5	3.36	1.02	6.5	2.84	0.72	5½
3	805	10.0	3.76	0.80	5.5	3.21	0.51	9
4	805	12.5	4.40	0.92	6.0	2.27	0.79	22
5	805	8.0	4.12	0.58	5.5	2.88	0.57	11
6	805	10.5	3.37	0.93	9.0	3.04	0.89	18
7	805	11.0	3.51	0.94	8.5	3.24	0.78	5
8	805	12.0	3.86	0.93	12.5	4.05	0.93	33; still living after 48 weeks.
9	805	12.0	4.01	0.89	11.0	3.98	0.82	2
10	630	11.0	3.61	0.91	10.0	3.70	0.81	0
11	805	13.0	4.25	0.91	7.0	2.55	0.82	9
12	280	12.5	4.15	0.90	10.0	3.66	0.81	5
13	805	11.0	3.67	0.90	9.3	3.22	0.85	4
14	805	12.0	4.02	0.89	8.0	3.05	0.78	25
15	210	10.5	3.64	0.86	7.5	3.14	0.72	3
16	805	11.0	3.62	0.91	6.0	2.88	0.62	3
17	535	10.0	3.86	0.79	9.3	3.36	0.82	1
18	642	11.0	3.10	1.06	9.2	3.55	0.77	2
19	175	9.0	2.99	0.90	9.0	2.65	1.00	4
20	280	10.5	3.69	0.85	5.0	2.45	0.61	13
21	175	8.5	3.34	0.76	5.5	2.61	0.63	7½
22	595	13.5	4.51	0.89	9.5	3.40	0.83	7; still living after 21 weeks.

TABLE 2.—SHOWING DEVELOPMENT OF ANEMIA AFTER LEAD TREATMENT IN A TYPICAL CASE (CASE 11).

Date, 1936.	Lead (mg.)	Hb. gm.	R. B. C. (millions)	Date, 1936.	Hb. gm.	R. B. C. (millions)
Jan. 31		13.0	4.25	Feb. 20	10.5	3.65
Feb. 3	35			Feb. 24	9.5	3.11
Feb. 4	...	12.5	4.27	Feb. 28	10.0	3.23
Feb. 5	70			Mar. 2	8.5	3.20
Feb. 6	...	11.5	3.90	Mar. 9	8.0	3.54
Feb. 7	105			Mar. 13	9.0	3.22
Feb. 8	...	12.0	3.83	Mar. 16	9.0	3.39
Feb. 10	140			Mar. 20	8.0	2.79
Feb. 11	...	11.5	3.89	Mar. 25	8.5	2.70
Feb. 12	140			Apr. 1	7.5	2.84
Feb. 13	...	11.0	3.50	Apr. 8	7.5	2.60
Feb. 14	140			Apr. 15	6.7	2.87
Feb. 15	...	10.5	3.59	Apr. 22	7.0	2.55
Feb. 17	140			Apr. 24	Expired	
Feb. 18	...	10.5	3.36			
Feb. 19	35					

Total 805

after the last dose of lead. In 3 cases such a significant decrease was not found until after 7 or 8 weeks. One patient developed anemia during the course of treatment and one showed an anemia 1 day after the last dose of lead. These 16 cases showed a pronounced drop in color index, which is attributed to the destruction of mature erythrocytes relatively rich in hemoglobin and their partial replacement by immature erythrocytes relatively deficient in hemoglobin. The immature cells include reticulocytes, polychromatic cells, stippled cells and nucleated red cells. With the exception of Case 5, there were significant decreases in the color index ranging from 0.04 to 0.30, with an average drop of 0.15 in color index during the interval from the first to the last count taken. Of the 6 cases which did not develop a significant anemia, 4 (Cases 9, 10, 17, 18) died within 2 weeks after treatment, 1 (Case 19) died 4 weeks after receiving only 175 mg. of lead, and 1 (Case 8) is still alive having developed no anemia following a full course of 805 mg. of lead.

2. *Anisocytosis and poikilocytosis* of varying degree were noted in practically all the films studied.

3. *Nucleated red blood cells* were found in the smears in 20 of the 22 cases studied. Of these 20 cases all showed normoblasts and 6 (30%) also showed megaloblasts. Of the total number of nucleated cells counted, 4% were megaloblasts. Normoblasts were noted as early as 8 days after the completion of treatment and as late as 4 months, the average time of their appearance being about 3 weeks. Two cases (Cases 10, 15) at no time showed nucleated red cells in their blood smears. One of these (Case 10) received 630 mg. of lead and died 2 weeks after the onset of treatment, while the other (Case 15) received but 210 mg. of lead and died 4 weeks after the initial treatment.

4. *Reticulocyte counts* were made in one typical case (Case 22, Table 3). It was found that the percentage of reticulocytes closely paralleled, and was somewhat higher than, the percentage of stippled cells on every occasion when the two counts were checked. In some cases reticulocyte counts of over 5% were found.

5. *Polychromasia* and *achromasia* were noted in most of the slides.

6. *The stippled cell counts* were made from smears treated with Wright's stain. In 18 cases this count was checked with the basophilic aggregate count in smears stained by Manson's borax-methylene blue method. A stippled cell count of 1% or over, which was taken as significant of plumbism, was found in 17 of our 22 cases, and was reached in from 1 to 8 weeks (average $3\frac{1}{2}$ weeks) after the start of treatment. The highest stippled cell count found was 15% (Case 11). Over 50% of nucleated cells showed basophilic stippling of their cytoplasm.

7. *The basophilic aggregation* stains were not satisfactory. There was difficulty in preventing precipitation of the methylene blue stain, particularly in warm weather. According to McCord *et al.*,

the basophilic aggregation stain reveals all the basophilic substance of the erythrocytes including the polychromatophilia, reticulation and the punctate stippling. Our tabulations show that the basophilic aggregation count instead of being higher than the stippled red count, was lower in most cases. In Case 22 the reticulocyte count was higher than the basophilic aggregation count on each of the 19 dates when the two counts were checked (Table 3).

TABLE 3.—COMPARISON OF PERCENTAGES OF STIPPLED CELLS, BASOPHILIC AGGREGATES, AND RETICULOCYTES (CASE 22).

Date, 1936.	Stippled cells (Wright's stain).	Basophilic aggregates (Manson's stain).	Reticulocytes (cresyl-violet stain).
July 21	1.2	0.77	1.4
July 24	1.5	0.73	2.2
July 27	1.0	0.88	2.2
July 28	1.2	0.77	2.2
July 31	1.4	1.10	1.8
Aug. 3	1.2	0.80	2.0
Aug. 5	1.2	0.91	2.2
Aug. 6	1.4	1.00	2.2
Aug. 8	0.8	0.71	1.6
Aug. 10	0.8	0.82	1.2
Aug. 11	1.8	0.75	1.8
Aug. 13	1.8	0.64	2.2
Aug. 22	1.2	1.10	1.4
Aug. 27	1.4	0.70	2.2
Aug. 31	4.4	3.20	5.0
Sept. 4	4.2	3.30	5.0
Sept. 9	5.6	3.30	5.4
Sept. 11	4.4	3.20	5.0
Sept. 14	5.6	4.80	5.8

8. *Cabot ring cells* were found 10 times in 6 cases. *Howell-Jolly bodies* were found twice.

Effect of Lead on the White Blood Cells. A. *Findings of Previous Workers.* The literature contains relatively few reports on the effect of lead intoxication upon the white cells and these reports are conflicting. In animal studies, McLean¹⁶ found an immediate neutrophilic leukocytosis which was followed in about 8 hours by an increase in lymphocytes and monocytes; Aub *et al.* found a lymphocytosis, while Ophüls¹⁶ found myelocytes in the peripheral circulation. In clinical cases, little effect on the leukocytes was noted according to Pepper and Farley.¹⁶ Biondi¹⁵ reported eosinophilia and mononucleosis but considered them as of only slight relative importance in plumbism. Bell *et al.*⁴ found that in patients with cancer a slight leukocytosis followed moderate doses of lead, and a marked leukocytosis resulted from large doses. The earlier the count was made after the injection the greater the likelihood of finding a leukocytosis. A relative lymphocytosis occasionally occurred and a slight eosinophilia appeared to be fairly common. Brookfield reported that in cancer patients with lead intoxication the only constant change was a tendency for an "increase" in monocytes of from 3 to 5%. Ferguson and Ferguson reported a

general shift of neutrophils to the right, in their cases of chronic plumbism among shipbreakers. Cadwalader⁷ reported myelocytes in the peripheral blood stream of a patient with lead intoxication.

B. *Findings in Present Study.* 1. *Leukocytosis* was noted in 14 cases (Table 4), in which it occurred 1 to 12 weeks (average 6½ weeks) after the beginning of treatment, or from 1 day to 8 weeks (average 3½ weeks) after the last treatment.

TABLE 4.—EFFECT OF LEAD ON WHITE BLOOD CELLS. NOTE THAT FIRST 14 CASES ONLY SHOW MARKED LEUKOCYTOSIS.

Case.	Lead mg.	Before treatment.						After treatment.						Weeks after treatment.
		Total.	Neut.	Ly.	Mon.	Eos.	Bas.	Total.	Neut.	Ly.	Mon.	Eos.	Bas.	
1	805	11,900	58	33	6	1		21,600	66	31	3	18
2	805	10,750	48	36	13	2	1	14,200	76	22	2	9
3	805	8,950	79	9	7	4	..	43,750	91	3	6	9
5	805	7,350	69	21	4	5	..	17,650	98	1	1	15
6	805	6,750	72	14	9	5	..	10,500	88	5	6	1	..	16
7	805	6,000	75	8	8	8	..	13,050	90	5	5	5
10	630	14,300	79	13	6	1	1	26,750	96	3	1	1 day
12	280	9,600	64	25	10	..	1	18,650	95	2	3	4
13	805	8,100	62	29	5	3	1	16,400	85	6	9	4
15	210	6,300	69	14	9	6	2	17,350	85	8	7	4
16	805	11,150	79	13	7	1	..	20,100	95	2	3	1½
18	642	8,500	83	10	3	4	..	24,550	92	3	5	2
19	175	3,100	70	14	8	8	..	8,550	91	2	7	4
21	175	12,700	78	12	7	3	..	21,350	81	6	13	7
<hr/>														
4	805	4,700	63	28	6	2	1	6,150	93	3	4	22
8	805	8,000	64	33	3	6,750	51	39	5	4	1	35
9	805	8,950	71	28	1	10,150	70	19	7	4	..	2
11	805	10,950	63	31	6	12,950	81	14	5	8½
14	805	10,400	37	50	9	4	..	7,700	60	36	1	2	1	28
16	805	11,150	79	13	7	1	..	12,400	88	6	6	4
17	535	23,550	81	10	7	2	..	18,100	94	2	1	3	..	1
22	595	9,700	76	20	4	5,550	64	30	5	1

2. *Differential Count.* The leukocytosis was associated with an absolute increase in number of neutrophils which rose to as high as 98% of the total white cell count. The lymphocytes were relatively and absolutely decreased in number to as low as 1% of the total white count. In no case was a lymphocytosis noted. Eosinophil and basophil counts were normal throughout. In one instance a slight monocytosis of 11% was noted.

3. *Basophilic Granulation of Neutrophils.* In all of our cases, after the beginning of treatment, there appeared an increase in basophilic granulations in the cytoplasm of the neutrophils. In some (Cases 6, 18, 19, 20) most or all of the neutrophils counted showed this granulation.

4. In 9 of our cases, *myelocytes* were noted in the peripheral blood. In 4 of these 9 the myelocytes made their appearance within 2 weeks after the beginning of treatment.

Summary. 1. Among 22 patients with advanced cancer, treated with colloidal lead triphosphate, a progressive anemia developed in most cases several weeks after the treatment had been completed. None of the cases showed a substantial improvement in the blood condition after cessation of treatment.

2. Nucleated red cells appeared in the peripheral circulation

almost simultaneously with the development of a moderate anemia, both appearing on the average about 3 weeks after the completion of treatment. Over 30% of the cases showing normoblasts also showed megaloblasts. Over 50% of all the normoblasts showed basophilic stippling of their cytoplasm.

3. The reticulocyte count closely paralleled the stippled red cell count. The reticulocyte count was a good measure of the bone marrow response to the anemia of the patient.

4. The basophilic stippled cells appeared in the peripheral blood at approximately the same time as the young erythrocyte forms. Stippled counts as high as 15% were found in some smears.

5. Counting of "basophilic aggregations" with the Manson stain was found to be unreliable. In only 25% of our counts was the basophilic aggregate percentage higher than the stippled cell percentage. The reticulocyte count was higher than the basophilic aggregate count on every occasion where the two were checked.

6. Cabot ring cells and Howell-Jolly bodies were noted occasionally.

7. Leukocytosis was noted in most of our cases and was usually marked. The average time of its appearance was $3\frac{1}{2}$ weeks after the onset of treatment.

8. Basophilic ("toxic") granulation was found in the cytoplasm of the neutrophils in all cases studied.

9. In 9 cases, myelocytes were found in the peripheral blood, 2 weeks or more after the beginning of lead therapy.

10. A relative and absolute lymphopenia was found in most cases, and in no instance was a lymphocytosis noted.

11. In 1 case a slight monocytosis was found.

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REFERENCES.

- (1.) Aub, J. C., Fairhall, L. T., Minot, A. S., and Reznikoff, P.: (a) Lead Poisoning, Baltimore, The Williams & Wilkins Company, 1926; (b) p. 140. (2.) Barga, J. A., Horton, B. T., and Osterberg, A. E.: *Am. J. Cancer*, 23, 762, 1935. (3.) Bell, W. B.: (a) Some Aspects of the Cancer Problem, New York, William Wood & Co., 1930; (b) p. 357; (c) p. 864. (4.) Bell, W. B., Williams, W. R., and Cunningham, L.: *Lancet*, 2, 793, 1925. (5.) Biondi, C.: Plumbism, *Internat. Labour Office Rev.*, Geneva, 6, 278, 1922. (6.) Brookfield, R. W.: *J. Path. and Bact.*, 31, 277, 1928. (7.) Cadwalader, W. B.: *Bull. Ayer Clin. Lab. of Penna. Hosp.*, 1, 44, 1906. (8.) Ferguson, A. E., and Ferguson, T.: (a) *J. Hyg.*, 34, 295, 1934; (b) quoted by Ferguson and Ferguson. (9.) Fleckel, I., and Tschernow, I.: *Zentralbl. f. Gewerbehyg.*, 7, 65, 1930, quoted by R. Jones, Ref. 11. (10.) Gulland, G. L., and Goodall, A.: *The Blood*, Edinburgh, Green, 1925. (11.) Jones, R.: *U. S. Pub. Health Rep.*, 48, 1011, 1933. (12.) Key, J. A.: (a) *Arch. Int. Med.*, 28, 511, 1921; (b) *Am. J. Physiol.*, 70, 86, 1924. (13.) McCord, C. P., Holden, F. R., and Johnston, J.: *Am. J. Pub. Health*, 25, 1089, 1935. (14.) Pappenheim, A.: *Fol. Haematol.*, 24, 86, 1919. (15.) Pearse, H. E.: *Arch. Int. Med.*, 37, 715, 1926. (16.) Pepper, O. H., and Farley, D. L.: *Practical Hematological Diagnosis*, Philadelphia, W. B. Saunders Company, 1933.

ACUTE HEMOLYTIC ANEMIA (LEDERER TYPE).

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THE hemolytic anemias belong to one of the most interesting but controversial and confusing chapters of clinical hematology. They include many varieties which have in common the process of intravital destruction of red blood corpuscles by excessive hemolysis. A considerable group of hemolytic anemias may be designated as "symptomatic." In these, the hemolysis is but a symptom of the underlying process which is mostly an acute intoxication by chemical poisons (lead, arsenicals, potassium, chlorate, etc.), bacterial toxins (sepsis, malaria, etc.), or certain drugs and foods. Another group represents a disease *sui generis*; the factor causing the hemolysis is here permanently present, a kind of constitutional dysfunction of the hematopoietic system. We have in this instance a constitutional damage of the produced erythrocytes thus markedly decreasing their vitality (congenital hemolytic icterus, sickle-cell anemia, etc.).

This paper will deal not with either of these groups, but with a variety recently recognized that may be considered as a well-characterized group.

Lederer,^{39a} in 1925, reported 3 cases of acute hemolytic anemia "probably of infectious origin." It occurred in 2 males and 1 female, the age ranging from 16 months to 25 years. The onset was characterized by rapid development of pallor, icterus, weakness, rise of temperature and evidence of hemolysis. The blood picture was dominated by a very profound rapidly progressive anemia with marked leukocytosis and erythroblastemia. A striking feature was the dramatic response to blood transfusion with prompt cessation of hemolysis and complete recovery.

A number of reports of this type of anemia has since appeared. No doubt this is not a new disease. The case of MacIntosh and Cleland⁴⁴ (1902) of rapidly increasing anemia with irregular pyrexia and death, and the 2 cases of Morawitz^{47a} (1907) of atypical grave anemia with recovery, appear to belong to this group of acute hemolytic anemias. He suggested an infectious agent as the cause of the acute destruction of the erythrocytes. Cases described under different titles, such as acute febrile, acute infectious anemia (Brill,⁷ Steffens,⁶³ Eimer,²¹ and others) and some of the reported recoveries from acute leukemia or "leukanemia" (Tecter,⁶⁵ Pearce,⁵⁹ and others) also appear to belong to this well-defined group of acute

hemolytic anemias. But due to diagnostic difficulties, this form of anemia has no doubt previously escaped recognition.

The following report is based on 3 cases of this kind of anemia.

Case Reports. CASE 1.—N. A., a white female child, aged 4 years, patient of Dr. K. T. Knode, had always enjoyed good health and since birth had been under his supervision. She was seen by him 2 weeks previous to the present illness, in a periodic visit to his office, apparently in good health. The present illness was preceded by a slight upper respiratory infection of several days' duration. On February 6, 1936, the child suddenly became ill with chills, fever, some vomiting and marked pallor. The skin was

TABLE 1.—BLOOD EXAMINATION IN CASES 1 AND 2.

Date.	Hb., %.	Hb., gm. (photometric).	Erythrocytes per c.mm., millions.	Color index.	Leukocytes per c.mm.	Myelocytes, %.	Neutrophils, %.	Lymphocytes, %.	Erythroblasts, %.	Reticulocytes, %.	Fragility of erythrocytes.	Bilirubin in serum (photometer), mg. %.	Van den Bergh direct.	Urobilin in urine.	Stained smears.
Case 1. 1936.															
Feb. 9	27	4.0	1.5	0.9	42.3	6	84	10	2.2	15.0	..	1.80	Weak pos.	++++	Red cells; marked anisocytosis, macrocytosis, polychrom.
10	19	2.9	1.3	0.7	28.0	6	82	12	1.7	..	Nor.	1.95	Weak pos.	++++	
*13	36	5.4	1.6	1.2	..	3	84	12	..	25.0	+++	Lets., marked shift to left.
*17	60	8.9	2.7	1.2	5.0	0	55	11.0	..	0.80	Neg.	+	
20	67	10.0	2.6	1.3	6.8	0	25	72	..	10.0	Nor.	Slight anisocytosis. No abnormalities.
24	85	12.7	4.3	0.9	5.5	2.0	
28	88	13.1	4.2	0.9	7.2	0	53	45	..	2.0	..	0.40	Neg.	Neg.	
Apr. 15	105	15.6	5.3	0.9	7.2	0	46	52	..	0.5	
June 20	108	15.8	5.4	1.0	8.0	0	58	42	No abnormalities.
Case 2. 1935.															
Nov. 10	27	4.1	1.7	0.8	45.0	10	82	8	4.2	28.0	..	2.80	Weak pos.	++++	Marked anisocytosis, many macrocytes, marked basophilic degeneration.
*18	39	5.4	2.2	0.9	31.5	6	77	13	2.2	20.0	Nor.	
21	43	6.4	2.3	0.9	14.9	4	79	17	1.0	9.5	..	1.50	Weak pos.	+++	
29	63	9.3	3.2	1.0	11.6	3	79	15	0.8	8.8	..	0.90	Neg.	..	
Dec. 3	69	10.3	3.5	1.0	8.9	0	67	25	0.1	4.5	..	0.40	Neg.	..	Normal.
1936.															
Jan. 3	103	15.4	5.2	1.0	12.7	0	70	23	..	0.5	..	0.20	Neg.	Neg.	
Apr.	104	15.5	5.3	1.0	10.8	0	70	30	Normal.
June	105	15.8	5.3	1.0	9.8	

* After transfusion.

definitely icteric, the urine dark reddish-brown and the temperature 102° F. Physical examination was essentially negative. On February 9, she was seen in consultation by one of us (A.S.G.). She appeared very apathetic; the skin was moist, pale and icteric. The sclerae were moderately yellow tinged. The blood count revealed marked anemia and leukocytosis with hemoglobin 27%, and evidence of regeneration, macrocytosis and hemolysis (Table 1). The urine showed a strong reaction for urobilin. The van den Bergh direct reaction was faintly positive and the serum bilirubin was 1.8 mg. %. The patient appeared critically ill and on the following day she was admitted to the Epworth Hospital, at which time the skin was still slightly icteric with extreme pallor. The liver and spleen were not palpable. The temperature was 104° F., pulse rate 130, and respiration 20 per minute. The hemoglobin had fallen to 19% (2.9 gm. %), erythrocytes 1.3 millions,

leukocytes 28,000 per c.mm. (differential count unchanged). The fragility test of erythrocytes was within normal limits. The serum bilirubin was 1.95 mg. % and the van den Bergh direct reaction was faintly positive. The blood culture was negative. The urine appeared to be bile tinged, but the bile test was negative. Albumen was 3+. Urobilin increased and the microscopic examination of the urinary sediment revealed many granular casts. In view of the critical condition the child was transfused with 200 cc. of her father's citrated blood. This treatment was followed by an immediate rapid improvement and the child's general condition became distinctly brighter. The skin was warm and moist. The temperature fell to 102° F. The same day intramuscular liver extract therapy was instituted and 2 days later another 200 cc. of citrated blood were given. The child made a speedy and complete recovery and left the hospital on the fifteenth day after admission. She has since remained in good health and the blood examination done 4 months later, June 29, 1936, revealed a perfectly normal blood picture (Table 1). Liver therapy was discontinued 1 month after discharge from hospital. There was no history of anemia, jaundice, or any blood disturbance on either side of the family and no history of drug-taking could be elicited.

CASE 2.—Mr. G., a white male, aged 40 years, superintendent of a factory by occupation and patient of Dr. M. Whitlock, was in good health until the present illness. The illness began about November 11, 1935, as a mild upper respiratory infection, for which he was treated by the usual medication. No improvement occurred during the next 5 days and on November 16, he suddenly became very weak with high fever, profuse perspiration, and dyspnea. He was admitted to the St. Joseph Hospital, Mishawaka, with a temperature of 104° F. When seen in consultation (A.S.G.), he appeared critically ill with a very anxious expression. The skin was pale, moist and icteric. The systolic blood pressure was 110 and the diastolic 65 mm. of mercury. Physical examination was essentially negative. His past history was irrelevant and there was no history of jaundice or anemia in the family. Careful inquiry revealed no history of contact with any dyes or special drugs. The blood showed a marked anemia and leukocytosis with evidences of regeneration and a predominance of macrocytes. The fragility of erythrocytes was not increased. The urine was highly colored and contained traces of hemoglobin. Albumen was 2+. Urobilin 4+. Urine sediment revealed occasional granular casts. The serum bilirubin was 2.8 mg. % and the direct van den Bergh reaction was weakly positive. The blood culture remained sterile. The patient belonged to Group IV (Moss) and on cross-agglutination it was discovered that he agglutinated the cells of all Groups IV, including his own cells. The specific autohemagglutination appeared at room temperature and disappeared by heating at 37° C. Because of this, the transfusion was given in gradual amounts beginning with 1 cc. of blood and gradually increased until the patient received 500 cc. of the citrated Group IV blood. This was followed by a mild immediate reaction, but the result of transfusion was phenomenal. The patient's temperature dropped and the general condition markedly improved. The worried expression disappeared. The following day intramuscular liver therapy was instituted and on November 18 the hemoglobin increased to 39% (5.85 gm. %), erythrocytes 2.2 millions, leukocytes 31,500 per c.mm. The differential count revealed no appreciable changes (Table 1). Examination of gastric juice revealed normal acid components.

The patient made an uneventful recovery and left the hospital after a stay of 19 days. He resumed his occupation and was last seen, June 19, 1936, in good health and the blood was normal in every respect. The phenomenon of the autohemagglutination persisted for 21 days and gradually disappeared.

CASE 3.—E. K., a white male farmer, aged 60 years, was admitted to the St. Joseph Hospital, Mishawaka, May 17, 1936, complaining of headaches, shortness of breath and occasional epistaxis of a few months' duration. His present illness began suddenly while working as usual on the farm. Since the onset he had been getting progressively weaker, had noticed a slight swelling of his ankles, and finally had to stop working. The family history did not reveal any history of jaundice or anemia. Physical examination on admission to the hospital revealed a well-built male, markedly dyspneic and appearing acutely ill. The skin was extremely pale with definite icteric tinge. Temperature was 102° F., respiration 22, pulse 90. The liver was palpable 3.5 cm. below the costal margin. The spleen was not palpable. On May 18, 1936, the blood picture revealed: Hemoglobin 25%, erythrocytes 1.45 millions, color index 0.89, leukocytes 7150 per c.mm. (77% neutrophils) and 3% myelocytes. Stained smears revealed considerable anisocytosis and slight poikilocytosis. Three days later, May 21, the hemoglobin was 21% (3.15 gm. %), erythrocytes 1.36 millions, color index 0.8, leukocytes 13,800 per c.mm. (94% neutrophils and 3% myelocytes). The platelet count was 250,000 per c.mm. Coagulation time was 6 minutes, bleeding time (Duke's method) 3. The urine was highly colored, the bile test negative, and the urobilin increased. The patient was treated with digitalis but did not make any improvement and expired on the fifth day after hospitalization.

Necropsy. The skin showed an extreme pallor with definite icteric tinge. Both nostrils were occluded by clotted blood. The tongue was dry and moderately coated but did not show any signs of glossitis. Lymph nodes were not palpable. On opening the body, the heart was found to be considerably enlarged with marked bilateral hypertrophy of the ventricles. The lungs were anemic and showed marked chronic emphysema. The spleen appeared slightly enlarged; its capsule contained numerous petechial hemorrhages. The liver was markedly enlarged and soft, of a chestnut-brown color with occasional light yellowish areas. The normal acinar structure was obliterated. The gall bladder was without evident lesion and the extrahepatic ducts were patent. The kidneys were normal in size and finely granular. Numerous petechial hemorrhages were present on the surface. The carefully searched gastro-intestinal tract was without evident lesion. The bone marrow of the femur was rather abundant, pinkish yellowish in color and somewhat gelatinous in consistency. Microscopic examination of the bone marrow showed a moderate but definite cellular hyperplasia involving both the erythropoietic and leukopoietic system. Section from the liver showed a marked parenchymatous degeneration, with necrosis of the liver cells surrounding the central veins. A large number of liver cells contained brownish pigment, most of which did not give the Prussian blue reaction for free iron and was apparently bile pigment. Section from the kidney showed a picture of chronic glomerulonephritis. The pathologic diagnoses were the following: (1) Eccentric cardiac hypertrophy with myofibrosis and sclerosis of coronary arteries; (2) anemia and chronic emphysema of lungs; (3) capsular hemorrhages of spleen; (4) acute parenchymatous degeneration of liver with retention of bile pigment (hemosiderosis?); (5) chronic glomerulonephritis with parenchymatous degeneration of kidneys; (6) hyperplasia of the bone marrow.

Discussion. Cases 1 and 2 present a rather typical picture of acute hemolytic anemia. The sudden onset, the rapid development of a severe anemia without an apparent cause, and the dramatic response to a blood transfusion with complete recovery are very characteristic. The highly colored, red, dark brown urine of Case 1

was most probably due to hemoglobinuria. In Case 2, the finding of hemoglobinuria was definitely established. The significance of the faintly positive van den Bergh reaction will be discussed later and it might be well to mention that this reaction was carried out by the ring-test technique (Elton²²) which seems to give more sensitive results.

Case 2 was complicated by the simultaneous occurrence of spontaneous autohemagglutination. The autohemagglutination is an exceptional hematologic phenomenon without a grave prognosis. The small number of cases reported up to date have occurred mainly in disease associated with severe liver damage (cirrhosis, etc.) in familial acholuric jaundice and in different kinds of blood dyscrasias (leukemia, pernicious anemia, agranulocytosis, etc.). The autohemagglutination is relatively frequently observed in diseases produced by trypanosoma. This report represents the first observation of autohemagglutination in acute hemolytic anemia of Lederer. The autohemagglutination disappeared after 3 weeks and was subsequently found negative on repeated occasions under different experimental conditions (cooling in the icebox, etc.). As illustrated in our case, autohemagglutination does not bar a blood transfusion, although the serum's autohemagglutination is associated with considerable iso- and heteroagglutinating properties (Bonnard⁶). The disappearance of autohemagglutination at the temperature of 37° C. may explain why this phenomenon did not occur within the body. As to the hemolytic properties of the autoagglutinating serum, the absence of auto- or isohemolysin seems to be constant (Bonnard⁶).

While Cases 1 and 2 are typical examples of acute hemolytic anemia, Case 3 is reported as a possible case. The somewhat incomplete data available make it difficult to come to a definite conclusion, but the sudden development of a grave anemia of the normochromic and macrocytic type, the associated icterus and the fatal exitus in the absence of transfusion as well as the necropsy findings in bone marrow and liver are suggestive. The possibility of a pernicious or a symptomatic anemia as the result of the chronic nephritis were also considered but dropped for lack of sufficient evidence.

A review of the literature gave 52 cases which may be regarded as belonging to Lederer's type of acute hemolytic anemia. Some were described under other titles, on the other hand, some of those described as Lederer's anemia did not appear to fit into this rather characteristic picture.

Age and Incidence. The acute hemolytic anemia of Lederer occurs at any age with possible predilection for the first 3 decades of life. The age of the reported cases ranges from 6 months to 60 years. There is no reason to assume that Lederer's anemia does not occur in infants under 2 years of age as suggested by O'Donogue and Witts.⁵² In fact, Lederer himself reported 2 cases in babies

6 and 16 months of age.^{39a,b} Both sexes seem to be equally affected. The scanty material available to date makes it difficult to make a definite statement as to the frequency of its occurrence; but there is considerable evidence to assume that this form of acute anemia is not a rarity but a disease of rather frequent occurrence.

Clinical Picture. The onset in typical cases is sudden, without any previous history of anemia or jaundice. Upper respiratory infection or sudden onset of general weakness and headaches or digestive disorders (vomiting or diarrhea) are frequent beginnings. An attack of abdominal pain may be an initial symptom simulating appendicitis (Parkes Weber⁷¹). Some atypical cases exhibit a sub-acute onset with prodromal symptoms such as: progressive fatigue, shortness of breath, occasional epistaxis, etc. After an incubation period of 2 to 6 days, a severe anemia develops accompanied by intensive pallor, icterus of varying degrees and a rise of temperature. The patient presents a picture of acute and critical illness with approaching coma or prostration. The air hunger, no doubt due to an acute anoxemia, is common. The temperature varies. In most cases there is a mild pyrexia, but temperatures of 104° F. are not infrequent. Physical examination reveals in some cases splenic and in others hepatic enlargement. The clinically demonstrable splenomegaly, however, does not necessarily belong to the picture of this disease. Occasionally cardiac manifestations are present (Manne and Kuskin⁴⁶) and hemic murmurs are frequently observed. Gastric analysis usually shows normal quantities of free hydrochloric acid and there is no evidence of Hunter's glossitis. The course is rapid and tends to a complete recovery or death within a short time. The rapidity of onset, course and recovery is so characteristic for this form of anemia that the French call it *anemie en coup d'archet* (Fiessinger, Decourt and Laur²³).

Hematology. The blood picture is characterized by rapid drop of erythrocytes and hemoglobin with appearance of immature and reticulated red blood cells with marked tendency to macrocytosis. The red blood count is usually below 2,000,000 and may be as low as 780,000 (Lederer^{39a}) or 600,000 per c.mm. (Manne and Kuskin⁴⁶). There is a pronounced anisocytosis, polychromasia, basophilic stippling and occasionally slight poikilocytosis. Cabot's rings are observed (Parsons and Hawksley,⁵⁶ Goudsmit²⁷). There are usually many nucleated red cells and the presence of megaloblasts is emphasized by Lederer.^{39b} O'Donogue and Witts⁵² denied in their paper the occurrence of megalocytes in Lederer's anemia, although in discussing some of the reported cases they mentioned that "nucleated red cells are usually present often in large numbers and typical megaloblasts can be distinguished among them." On the other hand, Parsons and Hawksley⁵⁶ are of the opinion that the anemia of their cases has constantly been of the megalocytic type, as shown by the high color index and the presence of megaloblasts and megaloc-

cytes in the peripheral blood. We believe that the tendency to macrocytosis together with the presence of many microcytes and rare poikilocytes is an important differential diagnostic point.

The marked regenerative activity is indicated by the presence of many reticulocytes, and nucleated red cells. The reticulocytosis may be as high as 64% (Fiessinger²³). The fall of the hemoglobin and of the red cells is usually proportional, but variations of the color index above and below unity are rather frequent. Lederer's anemia belongs generally to the normochromic type.

The anemia usually is associated with marked leukocytosis and often with a leukemoid reaction (Krumbhaar³⁵). The leukocytes may reach as high as 132,800 as in the case of Teeter.⁶⁵ In Lazarus'³⁸ case leukocytes were 108,000. O'Donogue and Witts⁵² found in 12 of the 36 collected cases white blood counts ranging from 20,000 to 50,000 per c.mm. The 6 cases reported by Lederer himself showed a leukocytosis from 20,000 to 81,000 per c.mm. A marked leukocytosis was also present in our 2 cases (42,000 and 45,000). The large numbers of nucleated red cells, which are so frequently present, have probably led in some cases to an erroneous estimation of the number of leukocytes. The possible counting of erythroblasts together with leukocytes also explains some unusual variations in the number of leukocytes in some of the reported cases (Eimer,²¹ Corelli¹⁴). Lederer^{39a} was apparently aware of that fact and suggested that correction should be made by subtracting from the total number of cells per c.mm., as estimated by the white blood pipette, the erythroblasts as estimated in the stained preparations. The leukocytosis is mainly due to neutrophils with a varying absolute shift to the left and the appearance of immature granulocytes. In Teeter's case⁶⁵ 10.75% of the white blood count of 132,800 were myelocytes and in our second case, the myelocytes constituted 10% of this white blood count of 45,000. In 1 of the cases of Parsons and Hawksley⁵⁶ the immature leukocytes of the granular series reached 30% of a white cell count of 35,000. This leukemoid reaction is an evidence of the simultaneous involvement of the leukopoiesis by the same etiologic agent and constitutes according to our opinion a characteristic feature of acute hemolytic anemia.

Occasionally, otherwise fairly typical cases, fail to show an appreciable leukocytosis (Joules and Mastermann,³² Altmann,² Holst³⁰ and others). Even the occasional occurrence of leukopenia and agranulocytosis is reported (Brill,⁷ Opitz,⁵³ Manfredini,⁴⁵ Goudsmit,²⁷ Planteydt.⁶⁰ In the case of Planteydt, the white blood count varied from 1710 to 3400 with 1 to 14% segmented leukocytes. The monocytes were not increased. The acute hemolytic anemia occurred here following a rheumatic infection which was treated with salicylates. In the case of Goudsmit²⁷ the white blood count was 1400 with 21 to 53% segmented leukocytes.

Hemolysis. Excessive destruction of the red blood corpuscles is a dominant feature in this form of anemia. Since we are unable to observe and measure the hemolysis as it occurs *intra vitam*, we must rely on indirect evidences. What are the evidences of hemolysis? The following are the most important:

1. *Hyperbilirubinemia.* Hyperbilirubinemia is a certain sign of hemolysis provided liver damage or obstruction to bile flow can be excluded. The quantitative determination of bilirubin in serum by means of the van den Bergh reaction needs a few remarks. There is considerable confusion in the literature on this point and the significance of the van den Bergh reactions has often been misinterpreted. Many reports on Lederer's anemia mention that the "indirect" van den Bergh reaction was positive. The mere statement of a positive "indirect" van den Bergh reaction is of no practical diagnostic significance. This "indirect" reaction, that is the test for small quantities of bilirubin in serum by means of an alcoholic extraction, is positive in most normal serums. This reaction is just a method for quantitative determination of bilirubin. The normal serum contains less than 0.25 mg. %. In Lederer's anemia it was found in amounts to 3.3 mg. % and higher (Holst³⁰). The presence of bilirubinates in serum gives the characteristic direct van den Bergh reaction which has definite diagnostic significance of liver damage. The finding of a considerably increased level of bilirubin in serum together with a negative or faintly positive direct van den Bergh reaction is suggestive of increased hemolysis. The hyperbilirubinemia in acute hemolytic anemia is partly due to excessive destruction of red blood corpuscles and partly to a definite liver damage on the basis of anoxic necrosis resulting from the severe anemia (Rich⁶²).

2. *Increased Excretion of Urobilin in Feces and Urine.* Urobilin (hydrobilirubin) is a derivative of the blood pigment and formed chiefly in the intestines. Its markedly increased excretion in the feces may be taken as evidence of excessive blood destruction within the circulation. Although the urobilin excretion does not parallel the blood destruction, its quantitative estimation in the feces is of importance in establishing a rough index for the rate of blood destruction. In the presence of an increased excretion of urobilin in feces, there is also an increase in the urine. If not due to excessive hemolysis, the urobilinuria is said to indicate some liver damage, that is, its incapacity to reconvert the reabsorbed urobilin into bilirubin. Urobilinuria and markedly increased excretion of urobilin in feces is commonly observed in acute hemolytic anemia. Lederer^{19a} reported a dilution value of 104,000 for urobilinogen and 240,000 for urobilin in feces (as against 6000 to 9000 dilution value as the upper normal limit).

3. *Hemoglobinuria.* In excessive hemolysis the unmodified blood pigment without the blood cells appears in the urine. In these cases

the reticulo-endothelial system is unable to transform the large quantities of freed hemoglobin into bilirubin and unmodified hemoglobin is excreted by the kidneys. In most of the acute cases of Lederer's anemia there is hemoglobinuria. Lederer³⁶ reported its occurrence in 2 instances. Parkes Weber⁷⁰ described his case as a "severe acute hemoglobinuria" and in the case of Castex, Steingart, and Poletti⁹ the hemoglobinuria was the dominating symptom of more than 1 week's duration.

4. *Abnormal Increased Blood Regeneration.* The highly increased regenerative activity of the hematopoietic system is evidenced by the presence of an excessive number of reticulocytes and a large number of erythroblasts in the circulation. This reaction is no doubt the normal response of the hematopoietic system to supplement the sudden loss of erythrocytes. The tendency to put out immature red blood cells is very marked in some of the observed cases. Fiessinger²³ found 3 to 5% of the erythrocytes to be normoblasts and Castex⁹ counted as many as 11,400 nucleated red cells per c.mm. Among them, 30% were normoblasts and 20% megaloblasts. In Teeter's case⁶⁵ there were 20,000 erythroblasts per c.mm.

5. *Fragility of the Erythrocytes.* Increased fragility suggests inherently weak cells (particularly in congenital hemolytic icterus); but, of course, a marked hemolysis may be present without any change in the resistance of the erythrocytes. In fact, our present knowledge does not afford any definite relation between the resistance of red blood cells to hypotonic salt solution and hemolysis as it occurs within the body. The resistance of red blood cells in acute hemolytic anemia is as a rule normal, but may be lowered in the active phase of anemia (Fiessinger,²³ Parsons and Hawksley,⁵⁶ and Lewis⁴²).

Diagnosis. The correct diagnosis of acute hemolytic anemia may present some difficulties; yet its recognition is of great practical importance in regard to prognosis and treatment. The diagnosis is based on the acute onset; rapid development of a severe anemia without any obvious cause; evidence of hemolysis; marked leukocytosis; macrocytic type of blood regeneration with marked reticulocytosis. The differential diagnosis includes: pernicious anemia, acute leukemia, congenital hemolytic icterus, erythroblastic anemia, "pernicious" anemia of pregnancy, simple achlorhydric anemia, aplastic anemia, and miscellaneous infectious diseases. Acute leukemia may be one of the most important and at the same time one of the most difficult of the differential diagnoses. The leukocytosis may in some true cases of Lederer's anemia be so marked as to present a leukemoid reaction. Many true cases of acute hemolytic anemia were thus misinterpreted as acute leukemias with recovery. Teeter's case⁶⁵ of a 6-year-old girl, suddenly taken ill with fever, vomiting and a severe anemia, is no doubt a typical case of acute hemolytic anemia. On the other hand, Parsons and Hawksley⁵⁶

described a case in a boy, aged 4, which appeared to be a fairly typical acute hemolytic anemia with recovery. Three weeks after the supposed recovery the boy was found to be suffering from acute lymphatic leukemia. The diagnosis of acute leukemia was confirmed at necropsy.

Hemolytic crisis in unsuspected familial acholuric jaundice may closely simulate Lederer's anemia. An illustrative case of this kind is described by Murray-Lyon.⁴⁹ Increased fragility would be an important differential feature in such cases.

Some authors have attempted to identify the acute hemolytic anemia of Lederer type with the so-called "pernicious" or "hemolytic" anemia of pregnancy (Witts⁷⁵). A great deal of evidence, however, speaks against this. Clinical observations suggest an intimate connection of the "pernicious anemia of pregnancy" with the mere fact of gestation. Many authors report the recurrence of anemia in subsequent pregnancies. Considerable evidence has been accumulated which justifies the assumption that the hyperchromic anemia of pregnancy is primarily due to a deficiency, probably of the antianemic substance and that the hemolytic destruction of the red blood cells is secondary. In India, where this form of pregnancy anemia is frequent and often fatal, it has been possible to establish a relation between it and the general nutrition, and to cure this anemia not only by liver extracts, but also by extracts of yeast (Wills^{73,74}). Both liver and yeast are known to possess large quantities of vitamin B. Ottenberg⁵⁴ classifies this "pregnancy pernicious anemia" among those due to a deficiency of the anti-anemic principle. As to the hematology, the blood picture may be identical with that of a true pernicious anemia. A leukocytosis is usually absent. The reticulocytosis is not marked in this anemia of pregnancy and only few normoblasts appear in the circulating blood.

For further differential diagnosis of anemias see the self-explanatory Table 2, in which only the most characteristic features are tabulated.

Prognosis. The prognosis of untreated Lederer's anemia is grave, but it is absolutely favorable when proper treatment is given at the right time. It seems that it also possesses some tendency to spontaneous recovery (Lewis⁴² and others).

Treatment. The treatment of choice is blood transfusion. The response to a single transfusion is often dramatic, followed by a complete recovery. Some authors believe the transfusion to be "specifically curative" (Ottenberg⁵⁴). In a few reported cases in which the death occurred in spite of blood transfusion, if the correct diagnosis is not to be questioned, we believe that transfusion was delayed until too late. One case is described where a severe rigor followed transfusion, with death occurring 3½ days later (Payne⁵⁸). Necropsy revealed massive "hemoglobin infarction" of the kidneys.

TABLE 2.—DIFFERENTIAL DIAGNOSIS OF ANEMIAS.

Disease.	Onset.	Erythrocytes.							Leukoocytes.	Bilirubin in serum.	Free HCl.	Other characteristics.	
		Hb. content.	Size and shape.			Blast forms.		Staining qualities.					
			Size.	Aniso.	Poik.	Normo.	Meg.	Poly.					B.St.
Acute hemolytic anemia	Acute	Usually normo- or hyper- chromic	Macros., ++ Micros., +	+++	=	+++	+	+++	+++	++	+	Rapid onset and course; recovery or death; fever.	
Pernicious anemia	Slow, progressive	Hyper- chromic	Megalos.	+++	+++	+	+	+	After liver +++	+	-	Tend. to remissions; response to liver therapy.	
Acute leukemia	Acute prodromal symp.	Variable	Normos.	++	++	++	+	++	++	+	+	Tend. to hemorrhage; fever; fatal course.	
Spherocytic jaundice (congenital hemolytic icterus)	May be acute (crisis)	Normo- chromic	Micros. (spherocytes)	+	=	=	-	+	+++	+	+	Predom. spherocytes; incr. fragility; hemolytic crisis; splenomegaly; fam. hist.	
Erythroblastic anemia	Acute	Normo- or hyper- chromic	Macros., ++ Micros., +	+	+	+++	-	+	+++	++	+	Racial incid.; bone invol. of skull and digits; mongolian facies.	
Pernicious anemia of pregnancy	May be sudden	Hyper- chromic	Macros.	+++	+++	+	+	+	After liver +++	+	+	Assoc. with preg.; compl. recovery with treat.	
Simple achlorhydric anemia	Subacute or chronic	Hypo- chromic	Micros.	++	++	=	-	-	+	-	-	Characteristic response to appropriate treatment.	
Aplastic anemia	Acute	Normo- chromic	Normos.	+++	+++	-	-	+++	-	-	+	Progressive fatal course.	

Abbreviations. Aniso. = Anisocytosis; Poik. = Poikilocytosis; Poly. = Polychromatophilia; B.St. = Basophilic stippling.

It appears to us questionable whether it was a true case of Lederer's anemia. The subacute onset, the absence of the nucleated red cells in the circulation, the normal Price-Jones curve of the red cell diameters and the necropsy findings do not seem to confirm this diagnosis.

The exact effect of blood transfusion is still an open question. Some authors believe that it causes a stimulation of the bone marrow (Morawitz,^{47a} Deneke,¹⁷ Leick⁴¹). Anders³ and Nather and Hickl⁵⁰ believe that the action of the transfused blood is not limited to the stimulation of bone marrow but that it also stimulates the antihemolytic property of the blood. According to Gross and Grätz,²⁹ the serum acts as in foreign protein therapy, having a stimulating action on the cytoplasm in general, while the red blood corpuscles act as transplanted cells. Kallius³³ believes that the favorable results of blood transfusions are due not to the transfused cells but to the serum. Curschmann²⁵ suggests that transfusion is a true substitution therapy, rather than a stimulating therapy and that transfusions relieve the bone marrow from an added load, thus causing a diminution of reticulocytes. Kühl³⁶ explains the action of transfusion on the basis that at first the entire hemolytic system has been blocked by the transfused blood, thus saving the red blood corpuscles of the patient from further hemolytic action. Secondly, the products of transfusion have a stimulating action on the bone marrow causing an elevation of red cells due to the bone-marrow reaction. Manfredini⁴⁵ essentially agrees with this point of view. We are inclined to assume with Kühl³⁶ and Manfredini⁴⁵ the importance of the antilytic action of the transfused blood. The transfused blood may contain an unknown substance which neutralizes the stimulating effect on the reticulo-endothelial system and stimulates the liver to produce the antianemic principle. The latter brings about maturation of the young cells. Thus the quick effect of transfusion may be explained. The transfused blood possibly also acts by checking the etiologic infectious agent.

As to the efficiency of the liver therapy in acute hemolytic anemia of Lederer, a considerable divergence of opinion prevails among the authors. Some found no response to the liver and regard this as an important differential point from pernicious anemia (Christiansen,¹¹ Joules and Mastermann³²). Other authors seem to have obtained favorable results with liver injections (Benhamou,⁴ Fiessinger,²³ Corelli,¹⁴ Vedel⁶⁹). The subject needs further investigation.

Pathologic Anatomy. The pathologic findings described so far in a relatively small numbers of necropsies do not present any particularly characteristic features other than evidences of severe anemia without an obvious cause. The liver, spleen, and kidneys generally give the Prussian blue reaction for free iron. The spleen is moderately enlarged and may show sterile infarcts. The liver is usually

more markedly involved showing varying degrees of acute parenchymatous degeneration with necrosis around the central veins. Rich,⁶² in a histologic study of livers associated with anemia of all kinds, noted that necrosis of liver cells in the central portions of each lobule was a constant finding and proportional to the degree of anemia. The cause of this lesion is postulated to be due to an insufficient number of oxygen-carrying cells (anoxemia). Similar changes in the liver have been produced experimentally by subjecting animals to low barometric pressures and low oxygen tension.

The bone marrow is usually hyperplastic, "maroon colored or like red-currant jelly" (O'Donogue and Witts⁵²). But occasionally in cases coming to necropsy the bone marrow may show some aplastic changes (Eimer²¹).

Moschcowitz⁴⁸ found in his case of acute febrile pleiochromic anemia hyaline thrombosis of the terminal arterioles and capillaries. This was particularly marked within the heart muscle. Whether his case truly belongs to Lederer's form of anemia appears somewhat questionable. Lederer^{39b} himself failed to see a resemblance.

Pathogenesis. We have described acute hemolytic anemia in its clinical, hematologic and pathologic manifestations and now have to raise the question as to its pathogenesis and position in the hematologic system.

We believe with most of the authors that there is sufficient evidence to justify consideration of Lederer's anemia as a "Hemolytic Anemia." Ottenberg⁵⁴ in his new classification of anemias gives to Lederer's anemia an independent place among anemias due to toxic destruction of blood by infections. Similarly Vaughan⁶⁸ classifies it as an "unexplained hemolytic anemia." A few authors, however, consider it the result of a disturbance in the formation of red blood cells, which by their vulnerability are destroyed in great numbers (Goudsmit²⁷). In this conception, we do not clearly see how to explain plausibly all the suddenness and rapidity of onset, course and recovery, which is so characteristic for this type of anemia.

A few authors regard acute hemolytic anemias as clinical varieties of pernicious anemia (Greppi and Semenza,²⁸ Campanacci).⁸ They describe cases with subacute or acute onset and a clinical picture resembling Lederer's anemia with recovery following transfusion and liver therapy. A striking feature in all these cases is the absence of free hydrochloric acid in the gastric contents associated with a leukopenia and tendency to mononucleosis. These features, characteristic for pernicious anemia, do not belong to the picture of acute hemolytic anemia. Troisier, Bariety and Brocard⁶⁷ reported a similar case which showed still more resemblance to pernicious anemia. There was a total achlorhydria even after histamine injection, the tongue resembled Hunter's glossitis and the leukocytes numbered 2000 to 3000 with 3 to 10% myelocytes and 32 to 40%

neutrophils. These cases may indeed represent typical febrile variations of pernicious anemia with long remissions obtained by liver therapy but it is entirely unjustified to draw from these observations the general conclusion denying the existence of such an entity as acute hemolytic anemia of the type Lederer and considering it a variation of pernicious anemia.

The infectious origin of acute hemolytic anemia is very suggestive, but attempts to cultivate a microorganism from these patients have completely failed so far. All blood cultures remained sterile. If we recall the extrinsic factors that may produce acute hemolytic anemias, we have to mention in addition to the chemical poisons certain foods and microorganisms. Among the foods there are certain kinds of hemolysis producing mushrooms and there exists in Italy a peculiar disease characterized by severe anemia of hemolytic type, which is due to ingestion of a kind of bean ("Favismo"). Among the microorganisms *B. welchii* and the hemolytic streptococcus are the most important.

Bartonella infection, in man known as Oroya fever or verruga peruviana,³⁴ presents several interesting features which justifies our brief consideration. Oroya fever, most commonly encountered in the western Andes, is an acute infectious disease characterized by extremely severe hemolytic anemia of the hyperchromic megalocytic type accompanied by fever and considerable leukocytosis. The causative organism, first observed by Barton in 1904 and isolated by Noguchi in 1926, is the so-called Bartonella bacilliformis which is now regarded as a bacterium. It belongs to a group of microorganisms, the parasitic nature of which has been proven during the last few years (Kikuth³⁴). A remarkable feature of this acute Oroya fever anemia is that it has, like the acute hemolytic anemia of Lederer, the tendency to spontaneous recovery without specific treatment. Can we not recognize some interesting parallels between Oroya fever and acute hemolytic anemia of the Lederer type? In future studies and observations on Lederer's anemia, the blood smears should be carefully investigated for possible bacteria-like inclusion bodies within the red blood cells.

The clarification of the etiology of the acute hemolytic anemia (Lederer type) will help to establish a definite independent place for this form of anemia in the hematological system. It already exists as a clinical and pathologic entity.

Summary. 1. Three cases of acute hemolytic anemia (Lederer type) are reported and the literature reviewed.

2. The general picture of the disease is drawn and the differential diagnosis discussed.

3. Acute hemolytic anemia is characterized by an acute onset with fever, rapid development of a severe anemia with the appearance of immature cells, marked reticulocytosis and leukocytosis and tendency to complete recovery. The dramatic response to a single

blood transfusion appears to be very characteristic. The anemia is usually of the normochromic type with marked tendency to macrocytosis.

4. It is suggested that acute hemolytic anemia is not a rare occurrence and that many cases of obscure anemia reported in the literature as well as reports on recovery from acute leukemia actually belong to this group.

5. The clinical recognition of Lederer's anemia is of greatest practical importance since the untreated disease has a high mortality rate while the prognosis of the treated disease is absolutely favorable. Blood transfusion is the treatment of choice.

6. The reported occurrence of spontaneous autohemagglutination in course of acute hemolytic anemia is observed for the first time.

7. Some theories as to the action of blood transfusion are briefly presented.

8. The etiology of acute hemolytic anemia is at present unknown but its infectious nature is very strongly suggested. A comparison with the acute hemolytic anemia of Oroya fever is made.

BIBLIOGRAPHY.

- (1.) Allan, W.: *Surg., Gynec. and Obst.*, 47, 669, 1928. (2.) Altmann, F.: *Ztschr. f. Kinderh.*, 53, 112, 1932. (3.) Anders: Quoted by Manfredini. (4.) Benhamou, E.: *Le Sang*, 3, 1, 1929. (5.) Benhamou, Jude and Gille: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 52, 1145, 1928. (6.) Bonnard, R.: *Le Sang*, 7, 807, 1933. (7.) Brill, I. C.: *Arch. Int. Med.*, 37, 244, 1926. (8.) Campanacci, D.: *Riforma med.*, 49, 753, 1933. (9.) Castex, M. R., Steingart, M., and Poletti, R.: *Le Sang*, 6, 589, 1932. (10.) Chevallier, P., Guillaume, A. C., and Jude, L.: *Ibid.*, p. 707. (11.) Christiansen, T.: *Acta med. Scand.*, 71, 472, 1929. (12.) Cibils Aguirre, R., Correas, C. A., and Murtagh, J. J.: *Arch. argent. de pediat.*, 5, 330, 1934. (13.) Cooley, T. B.: *Am. J. Dis. Child.*, 36, 1257, 1928. (14.) Corelli, F.: *Hæmatologica*, 17, 141, 1936. (15.) Gurschmann: Quoted by Manfredini. (16.) Davidson, L. S. P.: *Quart. J. Med.*, 25, 543, 1932. (17.) Deneke: Quoted by Manfredini. (18.) Douglas, A.: *Brit. Med. J.*, 2, 526, 1933. (19.) Dunlop, H. A., and Sanders, A. G.: *Lancet*, 1, 1169, 1934. (20.) Eastman, N. J.: *Internat. Clin.*, 2, 257, 1935. (21.) Eimer, K.: *Deutsch. Arch. f. klin. Med.*, 150, 162, 1926. (22.) Elton, N. W.: *J. Lab. and Clin. Med.*, 20, 817, 1935. (23.) Fiessinger, N., Decourt, P. H., and Laur, C. M.: *Le Sang*, 5, 257, 1931. (24.) Giordano, A. S., and Eager, D.: *Am. J. Clin. Path.*, 6, 286, 1936. (25.) Gittins, R.: *Arch. Dis. Child.*, 8, 367, 1933. (26.) Gloor, W.: *München. med. Wehnschr.*, 77, 1096, 1930. (27.) Goudsmit, J.: *Nederl. Tijdschr. v. Geneesk.*, 79, 554, 1935. (28.) Greppi, E., and Semenza, C.: *Hæmatologica*, 12, 77, 1931. (29.) Gross and Gratz: Quoted by Manfredini. (30.) Holst, P. F.: *Acta med. Scand.*, Suppl., 26, 469, 1928. (31.) Josephs, H.: *Internat. Clin.*, 2, 139, 1935. (32.) Joules, H., and Mastermann, L. M.: *Brit. Med. J.*, 2, 150, 1935. (33.) Kallius: Quoted by Manfredini. (34.) Kikuth, W.: *Proc. Roy. Soc. Med.*, 27, 1241, 1934. (35.) Krumbhaar, E. B.: *AM. J. MED. SCI.*, 172, 519, 1926. (36.) Kuhl, G.: *Ergebn. d. inn. Med. u. Kinderh.*, 34, 302, 1928. (37.) Kuhl: *Klin. Wehnschr.*, 10, 1053, 1931. (38.) Lazarus, S. D.: *Am. J. Dis. Child.*, 40, 1063, 1930. (39.) Lederer, M.: (a) *AM. J. MED. SCI.*, 170, 500, 1925; (b) *Ibid.*, 179, 228, 1930. (40.) Lehdorff, H.: *Med. Klin.*, 31, 74, 1934. (41.) Leick: Quoted by Manfredini. (42.) Lewis, J. T.: *Ulster Med. J.*, 5, 51, 1936. (43.) Lovibond, J. L.: *Lancet*, 2, 1395, 1935. (44.) MacIntosh, A. H., and Cleland, J. B.: *Australian Med. Gaz.*, 21, 462, 1902. (45.) Manfredini, B.: *La Clin. med. ital.*, 66, 878, 1935. (46.) Manne, A. S., and Kuskin, L.: *J. Pediat.*, 4, 789, 1934. (47.) Morawitz, P.: (a) *Deutsch. Arch. f. klin. Med.*, 88, 493, 1907; (b) *Deutsch. med. Wehnschr.*, 59, 560, 1933. (48.) Moschcowitz, E.: *Arch. Int. Med.*, 36, 88, 1926. (49.) Murray-Lyon, R. M.: *Brit. Med. J.*, 1, 50, 1935. (50.) Nather, K., and

- Hickl, J.: *Wien. klin. Wchnschr.*, 37, 359, 1924. (51.) Navarro, J. C.: *Arch. argent. de pediat.*, 5, 410, 1934. (52.) O'Donogue, R. J. L., and Witts, L. J.: *Guy's Hosp. Rep.*, 82, 440, 1932. (53.) Opitz, H.: *Fol. hematol.*, 38, 137, 1929. (54.) Ottenberg, R.: *J. Am. Med. Assn.*, 100, 1303, 1933. (55.) Parsons, L. G.: *Ibid.*, 97, 973, 1931. (56.) Parsons, L. G., and Hawksley, J. C.: *Arch. Dis. Child.*, 8, 184, 1933. (57.) Paterson, D.: *Proc. Roy. Soc. Med.*, 24, 1049, 1931. (58.) Payne, R. V.: *Guy's Hosp. Rep.*, 84, 65, 1934. (59.) Pearce, R. M.: *Brit. Med. J.*, 2, 282, 1930. (60.) Planteydt, J. M.: *Nederl. Tijdschr. v. Gencesk.*, 79, 4901, 1935. (61.) Poynton, F. J., Thursfield, H., and Paterson, D.: *Brit. J. Child. Dis.*, 19, 57, 1922. (62.) Rich, A. R.: *Bull. Johns Hopkins Hosp.*, 47, 338, 1930. (63.) Steffens, L. A.: *Minnesota Med.*, 11, 412, 1928. (64.) Swan, W. G. A.: *Newcastle Med. J.*, 13, 141, 1933. (65.) Teeter, C. E.: *J. Am. Med. Assn.*, 48, 608, 1907. (66.) Todd, J. C., and Sanford, A. H.: *Clinical Diagnosis by Laboratory Methods*, Philadelphia, W. B. Saunders Company, 1936. (67.) Troisier, J., Bariety, M., and Brocard, H.: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 51, 866, 1935. (68.) Vaughan, J. M.: *The Anemias*, New York, Oxford University Press, 1934. (69.) Vedel and Anselme-Martin: *Presse méd.*, 39, 154, 1931. (70.) Weber, F. Parkes: *Proc. Roy. Soc. Med.*, 25, 15, 1931. (71.) Weber, F. Parkes, and Bode, O. B.: *Klin. Wchnschr.*, 11, 336, 1932. (72.) Weil, P. E., Schreiber, G., and Gain, G.: *Le Sang*, 8, 344, 1934. (73.) Wills, L.: *Indian J. Med. Res.*, 21, 669, 1934. (74.) Wills, L., and Talpade, S. N.: *Ibid.*, 18, 283, 1930. (75.) Witts, L. J.: *Lancet*, 1, 601, 653, 1932.

SKIN IRRITATION AND CANCER IN THE U. S. NAVY.*

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THE object of the study is to ascertain first, whether a group of adults between 16 and 45 or 50 years of age, exposed intensively to open air, to sun rays and to salt water suffer from skin and lip cancer more than the average. Second, whether or not this group shows the same probability of dying from cancer of the inner organs as does the general population. Third, whether or not young men cured of a skin or lip cancer are later as much disposed to cancer of the inner organs and of the surface as men of the same age group.

These problems are important from the points of view both of the pathogenesis of cancer and of public health. Roffo² showed in systematic animal experiments the significance of ultraviolet rays in the genesis of skin cancer. He thereupon warns against too much sun bathing. It is also known, that in rural districts epitheliomata of the skin and lip are more frequent than in the cities. Whether there are any differences in the incidence of the inner cancers is not known, because of the quality of the reports of causes of death in rural areas.

* The publication has the approval of the authorities of the U. S. Navy.

The conditions in the Navy represent an experiment on human beings. The results of the experiment were studied on the histories of cancer collected in the Bureau of Medicine and Surgery of the U. S. Navy.

The morbidity and the mortality was calculated for the 8 years 1929 to 1936,* the figures so obtained being based on 875,000 person-years of active service. The observations regarding the distribution of cancer according to the organ and age were based on 469 cases.

Skin and Lip Cancer. Both the morbidity and the mortality of skin and lip cancer are very high. Among 100,000 active males—officers and men—there occurred annually 8.9 ± 1.0 new cases of skin or lip cancer (actually 78 cases), and there were 1.25 ± 0.39 deaths from each of these two types of cancer. Thirteen cases for which the onset of the illness was before 1929—either another primary tumor of the same organ or as the same tumor—are *not* included in the above calculation of morbidity. The mortality figure contains all cases with an onset of the illness during the active service.

The 11 deaths from skin and lip cancer occurred among the active, reserve and invalided. Two deaths with an onset of the carcinoma after the men were transferred into the reserve, are here not counted.

It may be of interest, that among the 9 fatal cases of skin cancer between 20 and 49, 5 cases were melanomata, whereas among the non-fatal cases melanoma was infrequent (only 1 case).

Applying the skin and lip cancer age specific death rates from the general mortality statistics of U. S. A.† to the particular age distribution of the total group of males in active service in the U. S. Navy, there would be expected 3.56 deaths from skin and lip cancer instead of the observed 11. The mortality from skin and lip cancer in the Navy was thus in 1929–36 about 3 times higher than in the civil population of comparable ages in the U. S. A.

In spite of the large probable error, the higher mortality from skin and lip cancer is by no means accidental, as is seen from the high morbidity, which is also, with due regard to the probable error, much higher than in the civil population.

The personnel of the Navy is continuously under intensive medical supervision. All modern diagnostic and therapeutic achievements are at their disposal. There are yearly thorough preventive examinations. Under these circumstances, the therapeutic results should be much better than in the civil population, at least so far as skin and lip cancer are concerned.

According to our figures the relation between the admitted and the fatal cases of cancer of skin and lip was in the years 1929–36 as 7 to 1 and 8 to 1 respectively,‡ whereas the same relation in the

* Exactly 7 years and 11 months, from January 1, 1929, to November 30, 1936.

† Skin + scrotum + lip. Skin, 1927–33; scrotum and lip, 1930–33.

‡ From Table 1, 2 b or 2 a and b.

civil population is according to clinical experience between 2 to 1 and 3 to 1.

TABLE 1.—CANCER OF THE SKIN AND LIP.

1. U. S. Navy, active males; person-years of observation, 1929-36	875,000
2. Cases of cancer of the skin and lip with the onset	
(a) Before 1929 and during active service	13
(b) 1929-1936 and during active service	78
3. Deaths (skin and lip) during 1929-1936 due to:	
2 a	6
2 b	5

A ratio of 50% cured cases indicates that the morbidity is twice as high as the mortality; a curability of 66.6% means that out of 3 ill cases 1 dies and 2 survive, and from a ratio of about 86% we learn that each death corresponds to 6 survivors.

Considering that the therapeutic results were much better than in the civil population and that in spite of this the mortality from skin and lip cancer was higher, it is concluded that the morbidity in the Navy is according to the next calculation (Table 2) about 7.5 to 9 times higher than in the civil population and about 22 times higher than the mortality from skin and lip cancer in the civil population of the same age distribution. The figures are so surprising that it is necessary to point out that in 70% of the cases the diagnosis was proved by biopsy, necropsy or death, and that in a certain part of the other cases the clinical history and the authorities in the American medical world who treated them are a guarantee that there was no mistake.

TABLE 2.—SKIN AND LIP CASES.

	U. S. (civil males)	U. S. Navy
Skin and lip cancer.	of the same age distribution as U. S. Navy active persons.	
If the mortality per 100,000 is	a	3.14 a
and		
the per cent of cured cases is	about 60 to 66.6	86
the morbidity per 100,000 is	2.5 a to 3 a	$7.1 \times 3.14 a = 22.4 a$

The Total Cancer Mortality. The total cancer mortality in the Navy was in the years 1929-36 very low. The age specific death rates are mostly even smaller than the official death rates of white males in the Registration Area of U. S. A., which reveal—as is well known—only a part of the real cancer mortality. The deficit of cancer deaths in the Navy is therefore very considerable.

During 1929-36 (up to November 30, 1936) there occurred in the Navy (a) 112 cancer deaths* belonging to persons on duty or to persons which at the onset of the illness were on active duty; (b) 202 cancer deaths† belonging to the inactive personnel, with the onset of the illness in the period of inactivity; (c) 3 cases of malig-

* In 102 cases a postmortem examination was performed.

† In 127 cases a postmortem examination was performed, in most of the other cases the diagnosis was proved by biopsy, operation or Roentgen rays.

nancies, one osteosarcoma, one of myxosarcomata and one melanoma which became invalided and up to now could not be followed up. They may be dead. Today we can only calculate the death rates from the active personnel (875,000 person-years of observation) and we hope to be able to extend this part of the study to the inactive group.

Table 3 illustrates the real and the calculated number of deaths by applying the age-specific cancer mortality rates of males in U. S. Registration Area for 1928-1932, and in New York City for 1920 to a population of the same size and age structure as the Navy. It is probable, that by applying the figures from New York or Chicago or Baltimore and so on from a more recent date, the deficit of cancers would be even larger than calculated here. On the other hand, it must be considered that in the population of New York in each age group itself the number of older people is relatively larger and of younger smaller, than in the Navy. Thus the real difference may be as large as in the table or even a little smaller than in Table 3.

TABLE 3.—REAL AND CALCULATED NUMBER OF CANCER DEATHS IN U. S. NAVY, ACTIVE PERSONNEL, 1929-1936.

			Calculated deaths by applying the age specific death rates of white males from	
			U. S. Registra- tion Area, 1928-32	New York City, 1920
Age, yrs.	Person—years of observation.	Actual deaths in the U. S. Navy.	to the actual number of observed years in the Navy.	
16-19 . . .	79,900	3	3.3	3.4
20-24 . . .	321,030	14 (+ 2?)*	17.0	16.0
25-29 . . .	195,900	13 (+ 1?)*	15.4	47.8
30-34 . . .	141,800	16	18.0	
35-44 . . .	109,680	31	33.1	55.3
45-54 . . .	23,375	26	24.6	44.3
55-64 . . .	3,300	10	8.9	17.8
Total cases . . .		113 (+ 3?)*	120.3	184.6
Skin and lip . . .		11	3.5 less than	5.0†
Without skin and lip . . .		102 (+ 3?)*	116.8	179.6
Mortality per 100,000 . . .		11.6 ± 1.0	13.3	20.4 ± 1.5

* The cases which could not be followed up.

† Not exactly known.

The first enlistment examination has certainly a selective effect and does eliminate persons with symptoms of serious illness, thus diminishing also the rate of cancer mortality in the immediately following years, *i. e.*, in the age groups 16-19 and 20-24. But in this group there seems to be no deficit at all. There appear to be no measures which could artificially diminish the incidence of

cancer among the personnel in the age groups 24-64. Therefore these differences have to be considered as real.

According to our calculation 44% of the expected deaths are lacking, in absolute figures: 78 or 75* cases. Nobody will think that this higher difference is due to better results, and it is not. (In another paper we shall deal with this question.) But it must be remembered that we have in this population in the same years of observation about 80 cases of skin and lip cancer more than were expected. The close numerical relation between the actual hypermorbidity of the skin and lip on the one hand and the hypomortality of all other cancers from the other, is striking.

Astonishing as these results may seem, they are in agreement with Peller's¹ previous results.

The diminished cancer mortality is not accidental: It appears rather to be the consequence of biologic changes due to the increased skin and lip irritation by factors that are not cancerogenous for the inner organs. Thus the number of curable tumors on the surface becomes more frequent, but at the same time the number of the inner tumors, which are in most cases fatal, becomes smaller. This diminishes the total cancer mortality *and saves the lives of a certain number of people*. At this moment it is not important, whether all the 44% were saved by the peculiar interference of the skin and lip, or only for instance 34%, the other 10% relying upon other factors (among them therapy). It is also not known whether the lives are saved forever from cancer or whether they will die later from another cancer. Unfortunately, it is until now impossible to calculate the mortality for higher ages of the inactive personnel of the naval reserve, which has an age distribution more favorable for attacking this problem. (Of 207 death cases in the reserve 163 died between 50 and over 90.)

The Ratio of Skin and Lip Among All Cancers. For all available mortality statistics only about 5% of the male cancer deaths were credited to the skin and lip, the percentage being smaller among young adults and rising in the higher age groups. In the U. S. Navy the situation is very different.†

In the Navy deaths from skin and lip cancers were in younger years relatively more frequent than later. The ratio of skin and lip thus drops from the high level at 20-49 to a low level at 60-69 in which age the per cent of skin and lip cancer is almost as high as in the general population.

The explanation is not difficult. In the age groups 20-49 the personnel of the Navy is more exposed to skin irritations than later.

* If the 3 cases which could not be followed up are also dead, then 42%, or 75 cases, are lacking. While this paper was in press 5 of these 7 cases were followed up; 1 of the 5 had died.

† This part of the study is based on 469 fatal cancer cases, partly from the years 1929-1936, partly from earlier years.

where a large part, being in the reserve, are not more exposed to the sun and other skin irritations than the civil population of the same ages.

TABLE 4.—AGE DISTRIBUTION OF CANCER MORTALITY.

Age, yrs.	Total num- ber of cancer deaths.	Deaths from skin and lip cancer.		U. S. A., ratio of skin and lip cancers (in per cent of all cancers).
		Absolute.	In per cent of all cancers.	
15-19	7	3.2
20-39	125	13	10.4	3.2
40-49	97	7	7.2	3.2
50-59	97	4	4.1	3.2
60-69	83	3	3.6	3.8
70 and over . . .	60	3	5.0	7.7

It is possible that all or a part of the older men, who in younger years were cured of a skin and lip cancer, might have in the ages above 60 produced a new primary tumor in the inner organs, because their skin or lip cancer which was provoked 20, 30, 40 or 50 years ago did not any longer protect them. Until now this problem has not been studied, neither systematically nor occasionally. But as the skin ratio in the age groups 60-69 and over 70 is not exceptionally low—it is almost normal—the mentioned supposition is not probable.

The Multiplicity of Primary Tumors Resulting From a Cured Former Cancer of Skin or Lip. Among our fatal internal cancer cases there were found 3 cases with a cured malignant growth on the surface before the inner malignancy, viz.:

1. 1916, a 52-year-old man, epithelioma of the skin between the eyebrows on the roof of the nose; Roentgen ray treatment; cured.—Seventeen years later (1933) he died from a squamous-cell carcinoma of the nasal septum.

2. 1926, a 66-year-old man, epithelioma of the skin, left cheek; Roentgen ray treatment; 1927 a recurrence, surgical treatment; 1929 a tumor mass sub-diaphragmatically located by roentgen ray; 1930 pains in epigastrium, difficulties of swallowing. In April, 1931, he died from carcinoma of the esophagus.

3. 1929, a 69-year-old man, epithelioma of the skin on the left arm; excised in June, 1929.—In September, 1930 ($1\frac{1}{4}$ years later) he died from a cancer of the lung.

It must be admitted that the third case is a very doubtful one. It is probable that the lung tumor existed longer than 14 months and that both the lung and the skin tumor were synchronous. It is well known that a part of the inner tumors exist for a long time without any clinical symptoms, being detected only accidentally or terminally.

Among the cases of fatal malignancy there were many cases with a previously treated *benign* tumor on the skin and also 2 cases with a small ulcer on the lip, which was suspected to be an epithelioma but proved to be benign. One, a fatal cancer of the tongue, had 7

years previously (at the age of 43) an ulcer on the lower lip, which was excised and showed histologically *no* evidence of malignancy. The other case, a person with carcinoma recti (aged 54 years) had 5 years previously a small fissure on the lip, which according to the consulting specialist was benign and healed under ultraviolet ray treatment.

We have not mentioned until now the cancer cases in the nursing corps of the U. S. Navy. They form a small group, not suitable for a statistical analysis. There are altogether 14 nurses with a cancer. In 7 cases it was a cancer of the breast, in 1 a cancer of the uterus. One of the 7 breast cases is of casuistical interest, representing a multiplicity of tumors in a combination seldom found in women.

In February, 1933, a 42-year-old woman with squamous-cell carcinoma of the breast, had mastectomy;—15 months later (May, 1934) hysterectomy because of uterus myomatosus. During the operation an adenocarcinoma (Grade III) of *both* ovaries was revealed; 4 months later a fibroadenoma of an accessory breast was excised.

In this as in the cases which are interesting from our point of view it must be remembered that according to clinical experience a case is classified as cured, only after an interval of 5 years without symptoms. It is impossible after 1 or 2 or 3 years to say that a patient is cured, even if he seems to be. It is also impossible to decide whether in the last quoted case (breast-ovary) the tumors were synchronous or metachronous. Evidently synchronous tumors are, it may be repeated, of no interest to us; therefore we did not mention them, in spite of the fact that they are also represented in our material. One of these cases of synchronous multiplicity showed the combination surface—inner organs (cancer of the lip and of the larynx).

In none of the internal cancers with an onset of the illness between 30 and 50 the history showed a previously cured skin or lip cancer.

Unfortunately, the histories in a larger part of the older cases are incomplete. They were not kept. Thus the material we may turn to account is small. In only 115 cases over age 50 is the calculation possible. Among these cases we found the quoted 3 cases with a previously cured skin or lip cancer. The expectation was sometimes higher. We should not forget that the material is too small to make definite calculations. A research on a large scale is necessary. But even if the difference between the real and expected figure would shrink, the question we have to study would be: how long do the cases live between the first and the second tumor?

Summary. 1. The peculiar conditions of life in the U. S. Navy—the prolonged exposure to the sun's rays, to open air and to salt water—are associated with (a) a skin and lip cancer frequency 8 times normal, and (b) a greatly diminished morbidity and mortality from all other cancers. About four-tenths of the men who would be

expected to die from an inner malignancy produced instead of this cancer a curable skin or lip tumor.

2. The mortality from skin and lip cancer is in the U. S. Navy about 3 times higher than in the average population (of the same age composition). Among the fatal cases melanoma predominates. The danger from epitheliomata is small.

3. It seems that only a small part of the cured skin and lip cancer patients produce later a tumor in the inner organs. This problem must be studied on a larger scale.

4. By exposing young men to strong skin irritations which are not carcinogenous to inner organs, the lives of some who would die from a cancer might be saved, at least for a certain number of years.

REFERENCES.

- (1.) Peller, S.: *Lancet*, 2, 552, 1936; *Klin. Wehnschr.*, 15, 217, 1936; *Human Biol.* 9, 57, 1937. (2.) Roffo, A. H.: *Lancet*, 1, 472, 1936.

THE TREATMENT OF HEMATEMESIS AND MELENA BY A CONTINUOUS ALUMINUM HYDROXIDE DRIP.

A REPORT OF 21 CASES.

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THE acute emergency of hematemesis presents a troublesome therapeutic problem to the physician and potentially serious danger to the life of the patient. Except when the bleeding is slight, hematemesis usually is caused by the opening of an artery or vein. Since the immediate aim of treatment is to stop the bleeding, the procedure is commonly the same, whatever the primary cause of the hemorrhage. In most instances, the bleeding ceases spontaneously, no matter what the treatment, even on bed rest alone, but a certain number of patients with this type of hemorrhage die. Various procedures have been advocated, with the hope of reducing the number in whom gastric hemorrhage results disastrously, but the mortality rate, even with modern methods of treatment is much higher than is realized generally.

The mortality rate has varied in different series of cases recently reported. Hinton¹¹ reported a fatal outcome in 20% of those patients with severe gross hemorrhage; Bulmer,⁶ in 10.7%; Chiesman,⁸ in 25%; Allen and Benedict,² in 14.5%; Aitken,¹ in 11%; Tidy,¹⁶ in 19%; Davis and Nevin,⁹ in 21%; and Burger and Hartfall,⁷ in 22.6%.

These figures present a challenge to physicians to attempt to reduce the mortality in this type of case. which is, as Rivers and

Wilbur¹⁴ have shown, preponderantly the result of a gastric or duodenal lesion. They found that 76.8% of patients with hematemesis have peptic ulcer, and 12.4% have carcinoma; the remaining 10% have some other cause to account for the bleeding.

Many physicians have been too ready to accept blood transfusion as the simple solution to the problem. Blood transfusion, even when repeated and with large quantities, is not the solution, though it may be accepted as a routine procedure. The aim of treatment must be to arrest the hemorrhage and to prevent its recurrence. Since more than three-fourths of such cases are caused by a peptic ulcer, it should be recognized that there is no better way to arrest the bleeding and prevent its recurrence than by promotion of the healing of the ulcer.

Various forms of treatment, aside from transfusion, have been used in hematemesis and melena and the statistics just cited show that they have not been spectacularly successful. Hemostatics were used by the older physicians without any convincing results. Epinephrin, which causes contraction of the blood vessels when applied locally, is of little value in controlling bleeding in the stomach because the drug is too greatly diluted by the gastric contents when taken by mouth. Intramuscular injections of whole blood, anticoagulants and snake venom, as well as other substances, have been advocated by various workers, but none of these remedies has proved generally efficacious. Gastric lavage, which has been practised sporadically for 20 years, is rarely needed. Either hot water or ice-cold water has been employed by some in washing the stomach. The protecting clot is likely to be dislodged by this method, and it takes a great deal of temerity to try it. Soper¹⁵ used gastric siphonage with a Levin gastro-duodenal catheter which was introduced through the nose. The continual withdrawal of gastric secretion, especially in the emergency associated with gastric hemorrhage, is unphysiologic and contraindicated because the usual loss of chlorides in hemorrhage and emesis, added to the loss of chlorides during the period of siphonage, may be of serious import.

Surgery has had a steadily diminishing number of advocates. Bevan,⁵ Balfour¹ and Lahey¹² all advise against immediate operation, but reserve intervention later for recurrent bleeding. Surgical intervention in gastric hemorrhage entails great risks. If the bleeding is caused by an acute peptic ulcer, operation is likely to be futile, because there is no external indication of the presence of an ulcer and the stomach must be opened to deal with the bleeding point. The search for this is so difficult that the ulcer often is not found. In such instances, the shock of the operation in addition to the prolonged hemorrhage is almost certain to result in the death of the patient. On the other hand, a chronic ulcer is easily found. However, even in the presence of a known chronic ulcer, operation is inadvisable, because the chronic ulcer may not be the source of the

hemorrhage. It is impossible to exclude in such cases a complicating acute ulcer which would probably never be found at operation. Exsanguinated patients, even when they receive blood transfusions at the time of operation, are poor surgical risks.

Recent evidence indicates that after hemorrhage from an ulcer, much acid still remains in the stomach, and if this is true, it should influence the treatment of acute bleeding. It is exceptional for a single hemorrhage from a peptic ulcer to lead to death. The striking fact about the fatal cases is that, in all of them, the hemorrhage continued or recurred in spite of medical treatment. The hemorrhage from a blood-vessel in the stomach ceases as suddenly as it begins, as soon as the vessel is plugged with fibrin. Destruction of this fibrin is the cause of recurrence of the bleeding. It seems reasonable to suspect that the acid gastric juice digests the plug of fibrin and thus opens the bleeding vessel anew.

In this connection it is interesting that Meulengracht¹³ of Copenhagen recently has treated hematemesis and melena by administering food, and, in the series of cases he reported, the mortality was much less than in other recorded series of cases of profuse gastrointestinal bleeding. In a group of 251 cases of severe hematemesis and melena in which this method was used, there were only 3 deaths, a mortality rate of 1.5%. Meulengracht contrasted the results in this series with those in a similar group of patients, admitted to the hospital in Copenhagen, whose treatment included complete abstinence from food. In the latter group the mortality rate was 7.9%. This author reported that feeding the patient who has hematemesis not only improves his general condition, but that in addition, the bleeding ceases more promptly than when food is withheld.

Meulengracht himself offered no physiologic explanation for this, but others, especially Alvarez,³ have commented that the success of his method probably results from the reduction of hyperacidity. Alvarez suggests that "while trying to avoid dislodging the clot by food or persistalsis, we have left the delicate fibrin at the mercy of strong, unbuffered gastric juice." He adds that "the fact that he (Meulengracht) has been so successful indicates that the danger of digesting the clot is greater than that of dislodging it mechanically."

If this be true, the treatment of hematemesis, then, should consist of a method which continuously protects the bleeding area from the corrosive action of the hydrochloric acid. In view of Meulengracht's results with feeding alone, it was felt that they might be improved still further by a method which would furnish continuous counteraction of acid activity and at the same time preclude the undesirable possibility, even though it be remote, of mechanical dislodgment of the clot. Since exceedingly satisfactory results have been obtained in a large series of cases of uncomplicated peptic ulcer with the continuous administration of colloidal aluminum hydroxide through an

indwelling nasal Levin tube, it was determined to try this method in the treatment of hematemesis.

The material used and the method of administration in cases of hematemesis are the same as those which have already been described for the continuous control of acidity in peptic ulcer.¹⁷ Colloidal aluminum hydroxide is a creamy white, gelatinous substance, mildly astringent and non-irritating. It is amphoteric, and hence

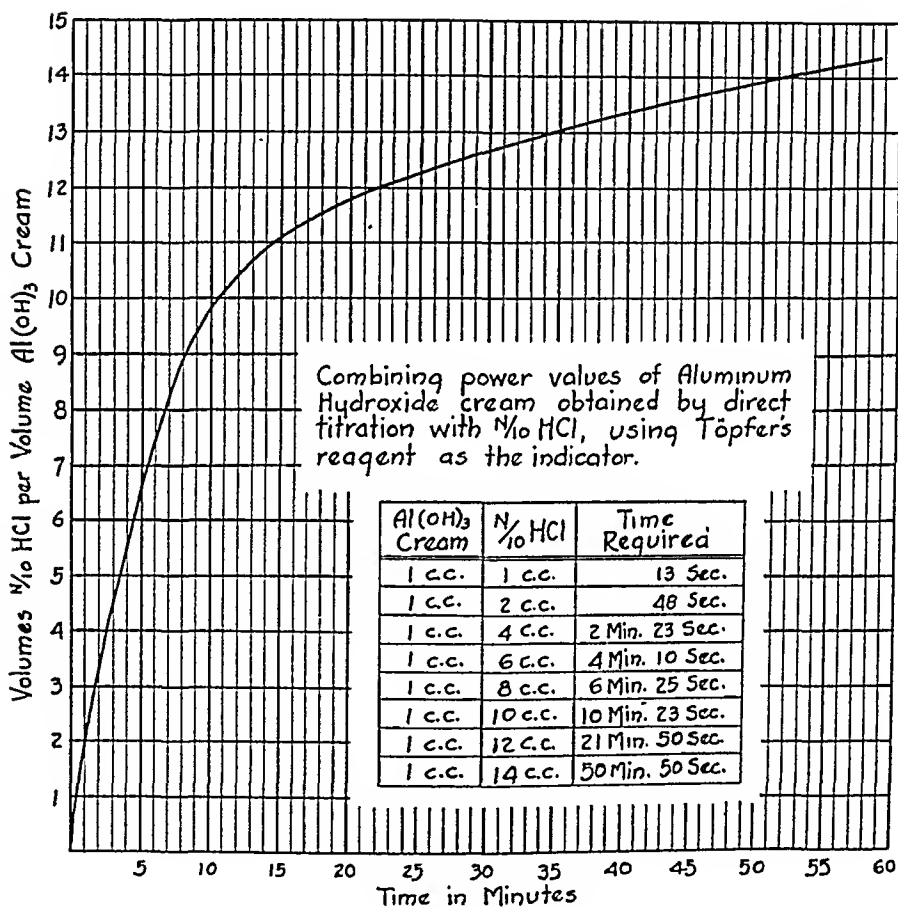


FIG. 1.—The combining power of colloidal aluminum hydroxide.

its continuous administration presents no danger of alkalosis. The preparation contains 5 to 6% of aluminum hydroxide and about 0.6% of sodium chloride. Experiments *in vitro* demonstrate that this colloidal product, when undiluted, combines with twelve times its volume of tenth-normal hydrochloric acid within half an hour (Fig. 1). Large doses of colloidal aluminum hydroxide do not disturb the acid-base balance of the blood, as shown by estimations of

the blood chlorides and the carbon dioxide-combining power and the pH of the blood.¹⁰ There is practically no absorption of aluminum from the gastro-intestinal tract. This substance, besides its exceptional antacid action, has the additional advantage that it protects the ulcer by coating it with a jelly-like mass, and by its astringent action assists in arresting the bleeding.

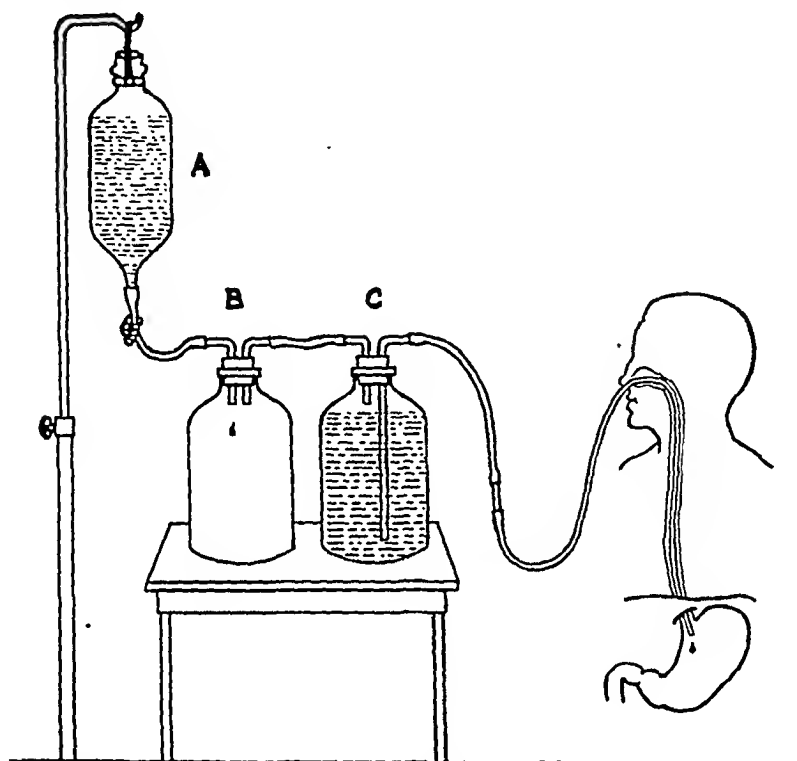


FIG. 2.—Flask A is filled with water, while clamp is closed. Bottle B is empty. Bottle C is filled with diluted (25%) colloidal aluminum hydroxide. The solution is allowed to siphon from Bottle C into a pan until it ceases. At this time there is a negative pressure created above the fluid level in Bottle C and also in Bottle B. The clamp beneath Flask A is adjusted so that the water will drip from Flask A into Bottle B at the rate of 10 drops a minute. Each drop creates an equivalent positive pressure in Bottle B and causes a drop to drip from the end of the Levin tube into the stomach. As the fluid level rises in Bottle B it causes the fluid level to fall correspondingly in Bottle C. The entire system must be air-tight at all times.

That it does actually prevent digestion of the fibrin clot has been shown experimentally. A clot of blood placed in a test tube filled with freshly aspirated gastric juice, and placed in an incubator at 37° C. shows evidence of digestion within 1 to 2 hours. However, when colloidal aluminum hydroxide is added to the tube containing the gastric juice and a small clot of blood, there is no evidence of digestion after 24 hours. Pepsin is not active in alkaline or neutral solutions. The optimum hydrogen-ion concentration for peptic digestion is between pH 2 and 3. When the pH of the solution is about 5, the power of pepsin to digest protein disappears.

A special apparatus for the continuous administration of colloidal

aluminum hydroxide had to be devised because this material is too thick, even in dilution, to flow through any tube constricted by a clamp to control the rate of flow. The apparatus consists of an elevated gravity flask filled with water, which is connected to an empty lower bottle by a rubber tube. The empty bottle is connected in turn to a siphon system which is filled with diluted colloidal aluminum hydroxide, and is connected to the indwelling nasal Levin tube. It is readily seen (Fig. 2) that the water inflow releases the siphon system outflow at precisely the same rate, that is, drop by drop. The system is automatic, simply requiring that it be kept air-tight and replenished with water and aluminum hydroxide solution each morning.

From September, 1935, to December, 1936, inclusive, 21 cases of hematemesis have been treated by this method in this hospital, with no deaths. This group includes only those patients who were admitted as emergency cases for the treatment of hematemesis as the leading often the only symptom. They vomited bright red or dark blood, or had tarry stools, in addition to secondary anemia sufficient to produce weakness, pallor, dyspnea or rapid pulse. Patients with blood-streaked or occasional "coffee-grounds" vomitus, occult blood in the stool or rare tarry stools were not included in this group.

In each case, as soon as the patient was admitted to the hospital, a Levin tube was passed through the nostril to the cardiac end of the stomach. This can be done without danger of injury to the bleeding area. The procedure will be effective even if the tube extends only to the lower end of the esophagus. If the tube reaches into the stomach, as shown by the withdrawal of gastric contents, it can be pulled up a few centimeters, so that the tip of the tube can not possibly cause any dislodgment of the clot or irritation of the bleeding point.

The proximal end of the Levin tube was connected to the drip apparatus which was regulated so that the colloidal aluminum hydroxide would flow into the stomach at the rate of 10 drops a minute. During the first 24 hours, the patient received 2 ounces of milk and cream every 2 hours. After that, the diet also included cooked cereals, gelatine, custards, cream soups, and rice and tapioca puddings.

Morphine was not used in this series of cases. Bulmer⁶ and others have expressed doubts as to the wisdom of the present use of morphine in these cases on the basis that excessive immobilization of the stomach may be definitely undesirable. Rest was promoted in these patients by the administration of barbiturates and sedatives of similar type.

In every instance the hematemesis ceased promptly, and there was no recurrence of the bleeding. The patients continued to receive the colloidal aluminum hydroxide by continuous drip both day and

night for 10 days. All of them left the hospital in good condition, and there has been no recurrence of hematemesis or melena in any case.

Although this series of cases of hematemesis is too small to justify any definite prediction as to the reduction of mortality in this condition, the results in each of 21 instances have been so satisfactory that the outlook seems definitely more hopeful than by any method previously reported. The results in these 21 cases represent considerable improvement over those previously recorded at this hospital. From January, 1931, to September, 1935, there were 38 patients admitted with acute gastric hemorrhage (Table 1). Of these, 11 died. Of the 11 fatal cases, necropsy in 5 revealed 4 instances of duodenal ulcer and 1 of gastric ulcer. Operation in 3 other cases showed 1 gastric ulcer and 1 benign neurofibroma with ulceration, and in the third case, no lesion could be demonstrated. In the remaining 3 cases, a duodenal ulcer had been demonstrated in the roentgenogram.

TABLE 1.—MORTALITY RATE FROM HEMATEMESIS AND MELENA (ST. LUKE'S HOSPITAL).

Year.	Cases.	Deaths.
1931	8	3
1932	11	2
1933	7	2
1934	6	3
1935 (January–August)	6	1

COLLOIDAL ALUMINUM HYDROXIDE DRIP INSTITUTED.

1935 (September–December) and 1936	21	0
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Since September, 1935, when the new treatment was instituted, there have been no deaths in 21 consecutive cases. Of this group, 15 had duodenal ulcer and 4 had gastric ulcer according to roentgenographic evidence. Two patients related a history typical of ulcer, but no lesion could be demonstrated in the roentgenogram.

It would seem that the continuous administration of colloidal aluminum hydroxide presents certain advantages over mere feeding of the patient with acute bleeding. Since the object in both types of treatment is to remove the excess acid in the stomach which is likely to destroy the fibrin plug in the bleeding vessel, it seems logical to suppose that a method which furnishes continuous antacid action by means of a powerful agent would be preferable to one which is able to neutralize lesser quantities of acid and that only intermittently, and which also presents some hazard of mechanical dislodgment of the clot.

Summary.—After treating a large series of patients with uncomplicated peptic ulcer by the continuous administration of colloidal aluminum hydroxide by means of a special drip apparatus, we tried the same method in 21 cases of severe gastro-duodenal hemorrhage, with complete recovery in every instance.

This method offers definite advantages over treating hematemesis by feeding, as advocated by Meulengracht who reported better results than in any recorded series of similar type and magnitude, because it goes a step further in furnishing continuous, rather than intermittent, decrease of acidity with a more powerful agent, and at the same time promotes the healing of the ulcer. That is, this treatment accomplishes a two-fold purpose; the arrest of bleeding and the protection of the ulcer to facilitate its healing.

REFERENCES.

- (1.) Aitken, R. S.: *Lancet*, 1, 839, 1934. (2.) Allen, A. W., and Benedict, E. B.: *Ann. Surg.*, 98, 736, 1933. (3.) Alvarez, W. C.: *Proc. Staff Meet., Mayo Clinic*, 11, 391, 1936. (4.) Balfour, D. C.: *J. Am. Med. Assn.*, 89, 1656, 1927. (5.) Bevan, A. D.: *Surg., Gynec. and Obst.*, 38, 358, 1924. (6.) Bulmer, E.: *Lancet*, 2, 720, 1932. (7.) Burger, G., and Hartfall, S. J.: *Guy's Hosp. Rep.*, 84, 197, 1934. (8.) Chiesman, W. E.: *Lancet*, 2, 722, 1932. (9.) Davis, T. A. L., and Nevin, R. W.: *Brit. Med. J.*, 2, 858, 1934. (10.) Einsel, I. H., Adams, W. L., and Myers, V. C.: *Am. J. Digest. Dis. and Nutr.*, 1, 513, 1934. (11.) Hinton, J. W.: *Ann. Surg.*, 93, 884, 1931. (12.) Lahey, F. H.: *J. Am. Med. Assn.*, 95, 313, 1930. (13.) Meulengracht, E.: *Lancet*, 2, 1220, 1935. (14.) Rivers, A. B., and Wilbur, D. L.: *Arch. Int. Med.*, 50, 621, 1932. (15.) Soper, H. W.: *J. Am. Med. Assn.*, 97, 771, 1931. (16.) Tidy, H. L.: *Lancet*, 2, 1365, 1934. (17.) Woldman, E. E., and Rowland, V. C.: *Am. J. Digest. Dis. and Nutr.*, 2, 733, 1936.

TUBERCLE BACILLI IN THE GASTRIC CONTENTS—AN IMPORTANT DIAGNOSTIC AND PROGNOSTIC FINDING.

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THE now widely used tuberculin test combined with Roentgen ray study of the infected, by means of the fluoroscope and roentgenogram, has made possible early discovery of pulmonary tuberculosis in the apparently healthy. These individuals usually will admit no symptoms. The physical examination of the chest frequently reveals nothing pertinent, and the temperature and pulse are normal. The pulmonary lesion may however be pathologically active, therefore of potential danger and in need of treatment; or it may be healed and in this instance a period of enforced rest would mean only an unnecessary loss of the individual's time. The problem then of the early infiltration is to determine its status at once, *i. e.*, is it pathologically active or is it healed?

In the past, recourse has usually been made to serial Roentgen ray films. Waiting for the roentgenogram to show change, is not without serious objections, for if progression must occur to determine activity at the cost of further lung destruction, valuable time has been lost by not having instituted treatment earlier, since

further extension necessitates a longer period of confinement. Extension furthermore makes the prognosis less favorable.

Fortunately at our command are certain laboratory procedures which make possible determination of the probable course of the pathologic process before the roentgenogram shows its spread or retrogression. These laboratory procedures are the blood sedimentation test; repeated study of the total and differential blood count; and the examination of the morning fasting gastric contents for tubercle bacilli. This report will concern itself with the study of gastric contents.

Methods. As part of the student health tuberculosis program, all students showing parenchymal pulmonary infiltration are requested to enter the University Infirmary for a 3-day period of observation and study. The temperature and pulse are recorded at 4-hour intervals. Total white and differential blood counts are done by a technician, especially trained in hematologic work; the blood sedimentation rate is determined. The morning fasting gastric contents are aspirated on 3 successive mornings. Usually from 10 to 15 cc. of gastric juice is obtainable. If nothing can be aspirated, 15 cc. of normal saline or water is placed in the stomach through the tube. After 15 minutes this fluid is again withdrawn. The stomach contents are sent to the laboratory where examinations are made by direct stained smears, cultures and guinea-pig inoculations.

In the laboratory the specimen is centrifuged for 1 hour at 2000 r.p.m. The supernatant fluid is poured off and smears are made directly from the sediment and stained for acid-fast bacilli. The remainder of the sediment is thoroughly mixed with an equal quantity of 10% (by weight) sulphuric acid and allowed to stand for 45 minutes with occasional shaking. It is then neutralized with 8% potassium hydroxide using brom thymol blue as the indicator. After neutralization the specimen is again centrifuged, the supernatant fluid is poured away and the sediment is divided into two equal parts. One part is used for cultures and the other for guinea-pig inoculation. The cultures are made by inoculating each of 2 tubes of Holmes coagulated egg medium with 0.5 cc. of the sediment. The culture tubes are stoppered with corks and are incubated at 37° C. for 3 to 4 weeks. Occasionally positive cultures are obtained in a shorter time. The remaining half of the sediment is injected intraperitoneally into a guinea pig which is watched for a period of 6 weeks, at the end of which time it is killed and examined for gross evidence of tuberculosis. If gross lesions are found, the diagnosis of tuberculosis is confirmed by the presence of acid-fast bacilli in stained smears made either from an enlarged lymph node or the spleen.

To prevent the possibility of outside contamination, the Rehfuess tube, syringe, and bottle used in obtaining the specimen are all sterilized by boiling. The reagent solutions are prepared with sterile distilled water, and sterile pipettes are used. It is very improbable that tuberculous infection of guinea pigs occurs in the animal rooms: The laboratory uses a large number of pigs each year to test the sterility of vaccines and the virulence of diphtheria organisms. On no occasion has tuberculosis been found in these pigs. Many pigs are also used by the laboratory to determine the presence of tubercle bacilli in urine. In no instance has tuberculosis been found in the guinea pigs where tuberculosis of the genito-urinary tract was not present. The opinion is therefore held that contamination is not a factor in the high incidence of tubercle bacilli found in the cases presented.

It is planned to aspirate a group of normal patients' gastric contents, inoculate pigs, and note results.

TABLE 1.—SPUTUM AND GASTRIC CONTENT STUDY.

Case.	Date.	Lesion.	Gastric contents.					Case.	Date.	Lesion.	Gastric contents.				
			Sputum.	Stain.	Culture.	Guinea pig.	Weight.*				Sputum.	Stain.	Culture.	Guinea pig.	Weight.*
1. 87056 Alb.	1935. 10-21	Mod. adv.	+	+	+	+	+10	16. 82513 Goos.	1936. 4-0 4-21 3-22	Minimal	-	-	-	-	+6
2. 84757 Silv.	10-26 10-27 10-28	Miliary tb. of lungs	-	-	-	-	+5	17. 10001 Holm.	4-23 4-24 4-25	Minimal	-	-	-	+	-12
3. 88688 Ptson.	11- 2 11- 3 11- 4	Far adv.	-	-	C	-	+4	18. 83312 Eli.C.	5-16 5-17 5-18	Minimal	-	+	+	+	+2
4. 87933 Hott.	11-11 11-12 11-13	Minimal tb. pneu.	-	-	C	-	0	19. 94089 M.Ett.	10- 8 10- 9 10-10	Mod. adv.	+	-	-	+	+8
5. 77272 St.	12- 9 12-10 12-11	Minimal	-	-	C	-	+7	20. 94490 Ma.Tre.	10- 8 10- 9 10-10	Minimal	-	+	+	+	+16
6. 76022 Stud.	12-19 12-20 12-21	Minimal	-	-	C	-	+10	21. 94383 R.Frie.	10-14 10-15 10-16	Minimal	-	-	C	+	0
7. 84566 Sven.	12-28 12- 9 12-30	Minimal	-	-	-	-	+4	22. 94875 N.Hard.	10-15 10-16 10-17	Minimal	-	-	C	-	0
8. 87362 Kalim.	1936. 1-25 1-26 1-27	Minimal	-	-	C	+	+10	23. 92787 Spson.	10-19 10-20 10-21	Minimal	-	+	+	+	-2
9. 79975 Grie.	2- 7 2- 8 2- 9	Minimal	-	+	-	+	-3	24. 93491 Sny.	10-19 10-20	Mod. adv.	+	+	C	+	-8
10. 79831 Ann.	3- 3 3- 4 3- 5	Mod. adv. 1 bac. seen in 3 stains	-	+	-	+	+18	25. 95181 Sode.	10-26 10-27 10-28	Mod. adv.	-	-	-	+	-2
11. 90446 Seib.	3- 3 3- 4 3- 5	Minimal	-	-	-	-	+2	26. 93631 Ander.	10-26 10-27 10-28	Minimal	-	-	-	+	-1
12. 89205 Wrol.	3- 9 3-10 3-11	Minimal	-	-	+	+	0	27. 92816 Shil.	10-28 10-30 10-31	Mod. adv.	-	-	C	+	+4
13. 32839 Maish.	3-21 3-23 3-24	Minimal	-	-	C	+	0	28. 93237 Suku.	11- 2 11- 3 11- 4	Minimal	-	-	-	-	+2
14. 88578 Homs.	3-28 3-29 3-30	Minimal	-	-	-	-	-2	29. 88261 Steff.	12-15 12-16 12-17	Minimal	-	-	C	+	+6
15. 77106 Lerq.	4- 9 4-10 4-11	Minimal	-	-	C	+	+4	30. 95381 Ega.	12-16 12-17 12-18	Mod. adv.	-	+	-	+	+9

C = Contaminated. Total positive 3 10 9 24 x
 * Weight change during year—x-18 gained 127 lbs., 7 lost 30 lbs., 5 no change. Y— Pig died.

Results. In Table 1 the 30 cases presented have shown Roentgen ray changes subsequent to animal inoculation thus indicating pathologic activity. All except Case 4 regarded themselves as well. This individual had a bizarre type of slowly resolving pneumonia, the etiology of which was finally determined by finding tubercle bacilli in the gastric contents. His subsequent course substantiated the diagnosis of tuberculous pneumonia. Of especial interest is Case 2 who had miliary tuberculosis of the lungs, bilateral tuberculous epididymitis, and tuberculosis of the prostate and right testis. On no occasions were there constitutional symptoms. Treatment consisted of a bilateral epididymectomy, unilateral orchectomy and sanatorium care. It will be noted that in Case 10 though only 1 acid-fast bacillus was seen by stain in 3 specimens, all 3 pigs showed tuberculosis following inoculation. It will be noted that only 7 of the 30 cases lost weight, while 18 showed a gain.

TABLE 2.—EXAMINATION FOR TUBERCLE BACILLI, SPUTUM VS. GASTRIC CONTENTS.

Lesion.	Gastric contents.							
	Sputum +.		Stain +.		Culture +.		Pig +.	
	No.	%	No.	%	No.	%	No.	%
Minimal (21)	0	0	6	28.6	8	38.1	15	71.4
Moderately advanced (7)	3	42.9	5	71.4	1*	16.7	7	100.0
Far advanced (1)	0	0	0	0	0	0	1	100.0
Miliary (1)	0	0	0	0	0	0	1	100.0
Total + tbc. (30)	3	10.0	11	36.7	9†	31.0	24	80.0

* 1 of 6 cases.

† 9 of 29 cases.

In Table 2 the 30 cases are summarized. Only 3 (10%) were positive by sputum examination. Especially significant is the fact that though all the minimal cases (21) showed negative sputum examinations, 15 (71.4%) were positive by gastric aspiration and guinea-pig inoculations. That the absence of tubercle bacilli indicates a good prognosis is suggested by the course of the 6 minimal cases showing negative gastric studies. Five of these showed constant Roentgen ray retrogression from the time of their discovery. One showed slight progression before the institution of bed rest. Four have continued to attend the university and show clearing of the lesions. Three of these 4 have subminimal lesions. The fourth, though strongly advised to withdraw when first found to have minimal tuberculosis (maximum in amount), has shown marked retrogression of his infiltration.

It will be noted that by culture fewer cases were found positive than by stain. The explanation lies in the fact that cultures are very frequently contaminated by yeasts and spore-forming bacteria found so constantly in the gastric contents. Because of this, examination in the future will be limited to study of the stain and guinea pig.

Neglected has been the use of gastric content examination as an important aid in determining when treatment may safely be terminated. With Roentgen ray study many cases of pathologically active pulmonary tuberculosis are found in the minimal or moderately advanced stage without the occurrence of symptoms or fever. Commonly, treatment of such cases either at home or in a sanatorium is uneventful, and because of splendid progress, unwarranted permission to return to former activities is frequently given. In addition to repeated study of the total and differential blood counts, and the blood sedimentation rates, examination of the gastric contents may frequently reveal the persistence of tubercle bacilli. The necessity of further treatment is then obvious. On three occasions students have returned to school following months of treatment, with apparent improvement, but with bacilli still present in the gastric contents. In each case physical activity resulted in extension of the tuberculous process. It is only reasonable, therefore, to insist as further evidence to support the assumption that the lesion is inactive, that the gastric contents be free of tubercle bacilli on repeated examinations.

Summary. 1. The increasing use of the tuberculin test combined with Roentgen ray examination of the infected make manifest many cases of asymptomatic pulmonary tuberculosis.

2. Laboratory procedures frequently make possible determinations of the status of the lesion before the roentgenogram shows a change.

3. Tubercle bacilli were found in the gastric contents in 15 of 21 (71.4%) minimal cases of pulmonary tuberculosis in which the sputum was negative.

4. The absence of tubercle bacilli in the gastric contents suggests an inactive lesion, or if active that the prognosis is good. Retrogression occurred in 5 of the 6 cases in this series without the institution of treatment, other than increased hours of rest.

Conclusion. The examination of the gastric contents for tubercle bacilli frequently gives positive evidence (71% in this series) that the minimal infiltration is pathologically active and in need of treatment. The procedure is of inestimable value in helping to determine, especially in the asymptomatic cases, how long active treatment should be continued. One of the criteria of a healed lesion is the repeated absence of tubercle bacilli in the gastric contents as indicated by guinea-pig inoculation. Strict adherence to this principle would result in fewer recurrences in the many patients with apparent but not real cures.

I wish to express my thanks and my appreciation to the staff of the State Laboratory of Hygiene for their coöperation and assistance in carrying out this work.

PROTAMINE-INSULIN AND INFECTION.* †

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INFECTION is a potent factor in diminishing the efficacy of standard insulin, for in diabetes complicated by infection,¹³ the dosage of insulin may be doubled or trebled, and yet fail to cause adequate combustion of carbohydrate. Similarly, in non-diabetics with infection, standard insulin, whether endogenous or injected, no longer exerts its usual effects on carbohydrate metabolism. The rôle of protamine-insulin in infection has not yet been studied, yet protamine-insulin, because of its prolonged action, will undoubtedly be widely used. It is therefore important to determine the effect of protamine-insulin during infection.

In an attempt to study its efficacy in the absence of diabetes, it was administered to 3 series of non-diabetic subjects, the first series consisting of 6 patients with tuberculosis, the second of 6 others with non-tuberculous infections, and the third of 4 individuals not suffering from infection. In general, the management of the patients began at about noon with dinner. Nothing further was ingested until 4 P.M.; when blood was drawn for glucose determination,⁵ and protamine-insulin was then administered. At 4.30 the patient took supper and blood was collected at 8 P.M., midnight, and at 8 A.M. without any further ingestion of food.

In the first series of patients with tuberculous infection 4 had far-advanced pulmonary tuberculosis, a fifth, tuberculous peritonitis, and the sixth, a combination of both. The results presented in Table 1 were obtained from a small girl of 9 years with tuberculous peritonitis. She received 15 units of protamine-insulin, a large dose for her weight of 44 pounds. Despite the relatively great dose, the effect of insulin was capable of reducing her blood sugar only to 102 mg. %. Four of the remaining 5 patients of this series exhibited the phenomenon of insulin resistance. Table 1 also contains observations on one of the control patients with arteriosclerosis, but without infection. His blood sugar fell to 57 mg. % by 8 A.M. This result is typical of the 3 other controls.

* The results have been described in part in an address by H. E. Himwich before the Pediatric Section of the Medical Society of the County of Kings, New York, December, 1936.

† The insulin used in this work was generously supplied by the Eli Lilly Company, and contained added zinc. It might therefore, be called protamine-zinc-insulin.

TABLE 1.—PROTAMINE-INSULIN IN TUBERCULOUS PERITONITIS AND CONTROL.

Time.	Diagnosis: 1. Arterio-sclerosis.		2. Tb. peritonitis.		Temp.
	Weight:	Blood sugar, mg. %.	Weight:	Blood sugar, mg. %.	
3:55 P.M.		96	44 lbs.	119	98.8
4:00					
4:30					
8:00		84		88	99.8
12:00		69		106	100.0
8:00 A.M.		57		102	98.6

Table 2 presents the observations on a little girl 2 years old, weighing 29 pounds, with acute tonsillitis. She is one of the second series of 6 patients with non-tuberculous infection, and received 4 units of protamine-insulin. Her blood sugar 18 hours later was 109 mg. %, and her temperature was high throughout the observations. However, a patient with carbuncle of the neck, and with no elevation of temperature, revealed a blood sugar of 101 mg. % 18 hours after the injection of 10 units of protamine-insulin (Table 2). Nevertheless, the other patients with insulin resistance that we observed did have fevers. Their respective diagnoses were malaria, localized peritonitis, mastitis and ureteral calculus.

TABLE 2.—PROTAMINE-INSULIN IN INFECTION.

Time.	Diagnosis: 3. Ac. tonsillitis.		4. Carbuncle (neck).	
	Dosage: 4 units P.I.	Weight: 29 lbs.	Dosage: 10 units P.I.	Weight: 120 lbs.
	Blood sugar, mg. %.	Temp.	Blood sugar, mg. %.	Temp.
3:55 P.M.	94	106.0	124	98.6
8:00	121	105.0	172	99.0
12:00	134	104.0	109	98.6
8:00 A.M.	109	99.0	101	98.2

In seeking controls without infection, a lad with a healing fracture of the tibia-fibula was examined who unexpectedly displayed insulin resistance. The observations were therefore to be repeated. The next day, however, he could no longer be called a normal control, for his temperature was 101°. Thus the insulin resistance of the previous day could be imputed to a developing infection.

The next experiment disclosed that hyperpyrexia, produced by diathermy, does not interfere with the hypoglycemic action of insulin. Standard insulin was used instead of protamine-insulin for two reasons: 1, protamine-insulin, as we have already shown, is not effective during infection, and 2, a more rapidly-acting insulin is required during the short 3-hour period of therapeutic diathermy. These results (Table 3) were obtained in an afebrile patient with chronic gonorrheal arthritis of the knee. The patient first had breakfast; hence the high initial blood sugar. Then he received 5 units of standard insulin before being subjected to diathermy for 3 hours. During this treatment, although his temperature was

raised to 104°, his blood sugar was reduced from 110 to 84 mg. %, a reduction which disappeared when the action of the standard insulin had ceased 3 hours later. The fall in blood sugar is significant, for diathermy of itself produces little, if any, change in blood sugar.⁸ The result is similar to that of a control receiving the same dose of insulin, but not subjected to diathermy. From these observations we may conclude that infection, not fever, is the potent factor in the development of insulin resistance.

Previous experiments of Corkill³ and other workers with standard insulin reveal that insulin resistance during infection is due largely to overactivity of the sympathetic nervous system and an excessive production of adrenalin. It remained to us to make similar studies with protamine-insulin.

TABLE 3.—DIATHERMY AND STANDARD INSULIN.

Time.	Control. Blood sugar, mg. %.	5. Gon. arthritis patient.	
		Blood sugar, mg. %.	Temp.
7:40 A.M.		—Breakfast—	
8:00	97	110	99.2
8:05		—5 units standard insulin—	
11:30	81	84	104.0
1:30 P.M.	132	92	101.0

TABLE 4.—ADRENAL DENERVATION AND INSULIN RESISTANCE. AVERAGE VALUES. (CAT).

Time, hrs.	Blood sugar, mg. %.		
	Control.	Toxin.	Toxin denervation.
0	79	131	114
3	31	73	91
6	41	75	24
9	80	93	Died of hypoglycemia
30		248	

In these experiments insulin resistance was developed in cats by the injection of 5 minimum lethal dose of diphtheria toxin* 18 hours before they received one-quarter unit of protamine-insulin per kilo. To exclude excitement the cats were narcotized with nembutal while blood samples were drawn. In the first column of Table 4, headed by the word "Control," are the average values obtained from the 3 normal cats; in the second, marked "Toxin," are the average values of the 3 cats that had received diphtheria toxin. The post-absorptive blood sugar at the beginning of the experiment is higher in the cats that had received diphtheria toxin, indicating the antagonism towards endogenous insulin. Furthermore, after the injection of protamine-insulin the level of blood sugar does not

* To Dr. A. F. Coea, of the Lederle Laboratories, and to Dr. H. W. Lyall, of the New York State Hygienic Laboratories, our thanks are due for supplying the diphtheria toxin used in these experiments.

fall to as low as a value in the animals that received the toxin, while the premortal rise brings their blood sugar to the high level of 248 mg.%. Additional experiments, however, were necessary to test the idea that the insulin resistance was due to overactivity of the sympathetic nervous system. For this purpose 2 animals were given diphtheria toxin after they had fully recovered from an operation in which the right adrenal was removed and a splanchnectomy performed on the left side to cut off the adrenal medulla from nervous stimulation. Both these animals succumbed to hypoglycemia. In the last column, are the results of one of these cats which disclose the mortal fall of blood sugar. Such an observation, in which insulin resistance is eliminated with denervation of the adrenal gland, offers unequivocal support of the idea that the chief mechanism of the antagonism is concerned with increased activity of the sympathetic nervous system, which favors glycolysis and thus raises the level of blood sugar.

TABLE 5.—ERGOTARTRATE AND INSULIN RESISTANCE. PROTAMINE-INSULIN $\frac{1}{4}$ UNIT PER KILO (DOG).

Time, hrs.	Blood sugar, mg. %.			Toxin ergotartrate.
	Control.	Toxin.	Toxin.	
0	102	88	87	100
1½	91
2	64
6	70	96	86	
9	102	86	93	

Ergotartrate prevents sympathetic activity. Unlike splanchnectomy, this drug does not diminish the secretion of adrenalin; however, it interferes with the response to adrenalin after its liberation from the adrenal gland. A study of insulin resistance was therefore made on a dog injected with ergotartrate. Four results are found in Table 5: first, the control, the normal response to one-quarter unit of protamine-insulin per kilo body weight with sugar falling from 102 to 70 mg.% in 6 hours. In the second and third columns, marked "Toxin," the reactions of the animal after receiving diphtheria toxin reveal definite resistance to the action of insulin, for the blood sugar rises. That this resistance is due to overactivity of the sympathetic nerves was demonstrated by the injection of ergotartrate. When ergotartrate was injected in a dose of 1 mg., repeated in 1½ hours, the usual response to insulin returned (last column). Even in the profound toxemia of diphtheria, protamine-insulin regains its potency when the sympathetic response is inhibited.

Insulin resistance does not appear to be due to the presence of antibodies, for antitoxin creates no insulin resistance. In Table 6 are seen the effects of the injection of protamine-insulin in a depancreatized dog receiving 330 antitoxin units. Insulin successfully

lowers blood sugar from 282 mg.% to 148 mg.% in 6 hours, and to 129 mg.% in 8 hours. Similarly, an injection of completely neutralized toxin-antitoxin mixture in no way interferes with the action of insulin. These results emphasize that with the neutralization of the toxin, preventing the stimulation of the sympathetic nervous system, insulin sensitivity returns.

TABLE 6.—HYPOGLYCEMIC EFFECT OF PROTAMINE-INSULIN AFTER INJECTION OF ANTITOXIN IN PANCREATIZED DOG.
(5 units protamine-insulin.)

Time, hrs.	Blood sugar, mg. %.	Blood sugar, mg. %.
0	282	208
	Antitoxin	Toxin- antitoxin
6	148	122
8	129	100

Cannon¹ has advanced the conception that adrenalin and the sympathetic nervous system mobilize the resources of the body in an emergency. For the organism to increase the level of the blood sugar in a non-diabetic condition affords a readily available source of energy to the body. This mobilization of carbohydrate, however, occurring in response to the emergency of an infection developing during diabetes is no longer beneficial because it intensifies the diabetic condition. Thus this ordinarily defensive reflex mechanism, becomes injurious in the special condition of diabetes.

Adrenalin is not the only antagonist of insulin. The grave effects on the course of diabetes of an intercurrent hyperthyroidism are well known, and there is ample evidence indicating increased activity of the thyroid gland during infection.⁹ The synergistic effects of the secretions of the thyroid and adrenal medulla are apparent in every case of hyperthyroidism which displays signs of hyperactivity of the sympathetic nervous system. Most important in this connection is the high level of blood sugar occurring so frequently in Graves' disease. In regard to effects on carbohydrate metabolism, thyroid therefore acts synergistically with adrenalin.

At least one other gland is important in the study of insulin resistance, namely, the anterior pituitary. As a result of the work of Houssay⁶ and others, it is now held that the anterior pituitary gland contains a hormone which raises blood sugar. With increased secretion of the anterior pituitary gland insulin resistance should therefore develop. Whether one accepts the point of view of Corkill, Marks and White,⁴ that the hormone of the anterior pituitary gland and adrenal medulla are synergistic in mobilizing liver glycogen, or that of Lucke, Heydemann and Hahndel¹¹ that the anterior pituitary functions *via* the adrenal medulla, it is apparent that both glands may act together to counteract the effect of insulin on blood sugar.

A review of the literature reveals that the diphtheria toxin exerts a direct necrobiotic effect on the islands of Langerhans¹⁴ and the cells of the liver.¹⁵ Moreover, the possibility exists that insulin is destroyed as a result of infection.⁷ Nevertheless, the chief factor in insulin resistance is hormonal antagonism. This conception is presented in diagrammatic form (Fig. 1). Physiologically, the brain may send impulses by way of the splanchnic nerves to the adrenal medulla, there to excite the secretion of adrenalin which,

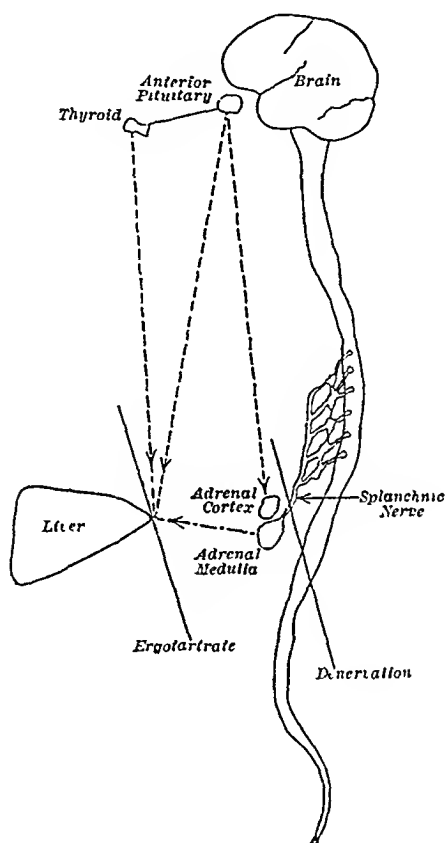


FIG. 1.—Hormonal antagonism to insulin.

in its turn, causes a breakdown of liver glycogen, and therefore an increase of blood sugar. The thyroid gland acts synergistically with the adrenal, as does the anterior pituitary, either directly or by way of the thyroid and adrenal cortex,¹⁰ which may also influence carbohydrate metabolism. During infection the adrenal gland, the thyroid and anterior pituitary glands are all stimulated directly by the toxin. In a similar manner, as a result of the direct excitation by the toxin, cerebral activity may be increased and additional impulses sent to the adrenal gland by way of the splanchnic nerves

thus originating in the central nervous system a reflex resistance to the action of insulin.

Once set into operation it is difficult to inactivate the mechanism of insulin resistance. Ergotartrate is not advisedly employed. Although its successful therapeutic use has been reported, the dosage must be relatively large and therefore is not safe.⁹ Denervation of the adrenal gland is not to be considered for several reasons which need not be discussed at this time. If signs of thyroid overactivity are present, the condition may be treated according to the accepted methods for the management of hyperthyroidism. It has been reported¹² that insulin resistance has been diminished by subjecting the anterior pituitary gland to radiation. However, this field is still largely experimental.

Since the hormonal response to infection cannot be controlled, it is preferable to go to the root of the trouble and combat the infection directly. In any case of insulin resistance a thorough search for the etiologic cause must be made in order to eradicate it. If this can be done surgically, there should be no procrastination. When surgical intervention is impossible or a general infection develops we have recourse only to increased insulin dosage, to be given more frequently.² Standard insulin may be preferable here because its more intense action is desirable in attempting to overcome insulin resistance. Furthermore, the administration of large doses of protamine-insulin is dangerous. Due to the prolonged activity of protamine-insulin it is possible that with improvement of the patient's condition a sudden decrease in insulin resistance may leave in the patient excessive amounts of active protamine-insulin.

Summary. Resistance is developed against protamine-insulin in non-diabetic patients with infection. The effect of the disease, in stimulating the endocrine glands and the nervous system, results in a rise in blood sugar, counteracting the effects of insulin whether endogenous or injected. It is suggested that standard insulin, with its more intense and rapid action, is preferable to protamine-insulin in cases of acute infection.

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REFERENCES.

- (1.) Cannon, W. B.: *Ann. Int. Med.*, 9, 1453, 1936. (2.) Clark, B. B., Gibson, R. B., and Paul, W. D.: *Arch. Int. Med.*, 56, 360, 1935. (3.) Corkill, A. B.: *J. Physiol.*, 75, 381, 1932. (4.) Corkill, A. B., Marks, H. P., and White, W. E.: *Ibid.*, 80, 193, 1934. (5.) Hagedorn, H. E., and Jensen, B. N.: *Biochem. Ztschr.*, 135, 46, 1923. (6.) Houssay, B. A.: *New England J. Med.*, 214, 1137, 1936. (7.) Karelitz, S., Cohen, P., and Leader, S. D.: *Arch. Int. Med.*, 45, 546, 1930. (8.) Krusen, F. H.: *J. Am. Med. Assn.*, 107, 1215, 1936. (9.) Lawrence, R. D., and Buckley, O. B.: *Brit. J. Exp. Path.*, 8, 58, 1927. (10.) Long, C. N. H., and Lukens, F. D. W.: *J. Exp. Med.*, 63, 465, 1936. (11.) Lucke, H., Heydemann, E. R., and Hahndel, H.: *Ztschr. f. d. ges. exp. Med.*, 91, 492, 1933. (12.) Pieri, J., and Sarradon, P.: *Bull. et mèm. Soc. mèd. d. hôp. de Paris*, 84, 1579, 1935. (13.) Rabinowitch, I. M.: *Canadian Med. Assn. J.*, 14, 481, 1924. (14.) Root, H. F., and Warren, S.: *Boston Med. and Surg. J.*, 194, 45, 1926. (15.) Stewart, H. J.: *Arch. Path.*, 7, 601, 1929.

ARTERIAL HYPERTENSION.

THE SITE AND SIGNIFICANCE OF THE HIGH CHLORIDE CONTENT OF THE BLOOD.

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It has long been known that the chloride content of the blood of patients suffering from essential arterial hypertension is usually increased; but, so far as we are aware, the site of the increased chloride and its significance are unknown. Our work is an attempt to throw some light on these problems.

Methods. *A. Chloride and CO₂ Capacity of Plasma and Red Cells.* Blood was drawn from the median-basilic vein without stasis into a 30 cc. Record syringe containing sufficient potassium oxalate as anticoagulant, from 3 series of fasting individuals: (a) 103 young healthy subjects, including 5 women; (b) 13 elderly people with normal blood pressure, mostly women, as controls, and (c) 48 patients who, on repeated examinations had marked arterial hypertension, of whom 40 were women. All individuals with signs of renal disease, as indicated by albuminuria or MacLean's urea concentration test, were rejected. The elderly control group was included in order to determine whether the difference of age between groups (a) and (c) was a factor in the causation of their blood-chemistry differences.

The whole blood was then brought into equilibrium with alveolar air by the method described by Van Slyke.^{11a} A portion was next transferred under oil, without loss of CO₂, to a centrifuge tube, centrifuged for 1½ hours and the plasma separated. The following were then determined:

1. The chloride content of both whole blood and plasma (methods of Myers and Short⁸ and of Van Slyke^{11b}).
2. The CO₂-combining power of both whole blood and plasma.^{11a}
3. The relative volumes of corpuscles and plasma in the whole blood. (Hematocrit. Evans⁴).
4. The CO₂-combining capacity and chloride content per 100 cc. of red cells (by calculation from 1, 2, and 3).

When we had sufficient blood, all estimations were made in duplicate. This applies to the great majority of our figures.

Each red cell volume figure is the average of 4 determinations. We are aware of the difficulties in determining the true red cell volume % by any hematocrit method, as has been well shown by Ponder and Saslow.⁹ Since however, their more accurate method requires 35 cc. of blood in addition to that required for chloride and CO₂ concentrations, it was obviously undesirable to use this method with human subjects. We were more concerned with showing comparative changes in the blood of each subject at various times, and as we used the same method for all (1600 revs. per min. for 1½ hours, in uniform bore hematocrit tubes) we feel, as indeed these authors state, that the hematocrit method is valuable for the determination of relative changes in cell volumes.

Another source of difficulty is the inaccuracy of many of the methods of chloride estimation in use. This has been well shown by Greenwald and Gross' comparison of methods.⁵ We therefore used two methods, viz.: that of Myers and Short⁸ and that of Van Slyke,^{11b} in both our normal and hypertension groups, and, although the figures given by each differ, the differences brought out by each method between normal people and hypertension patients were found to be of the same kind (Fig. 1).

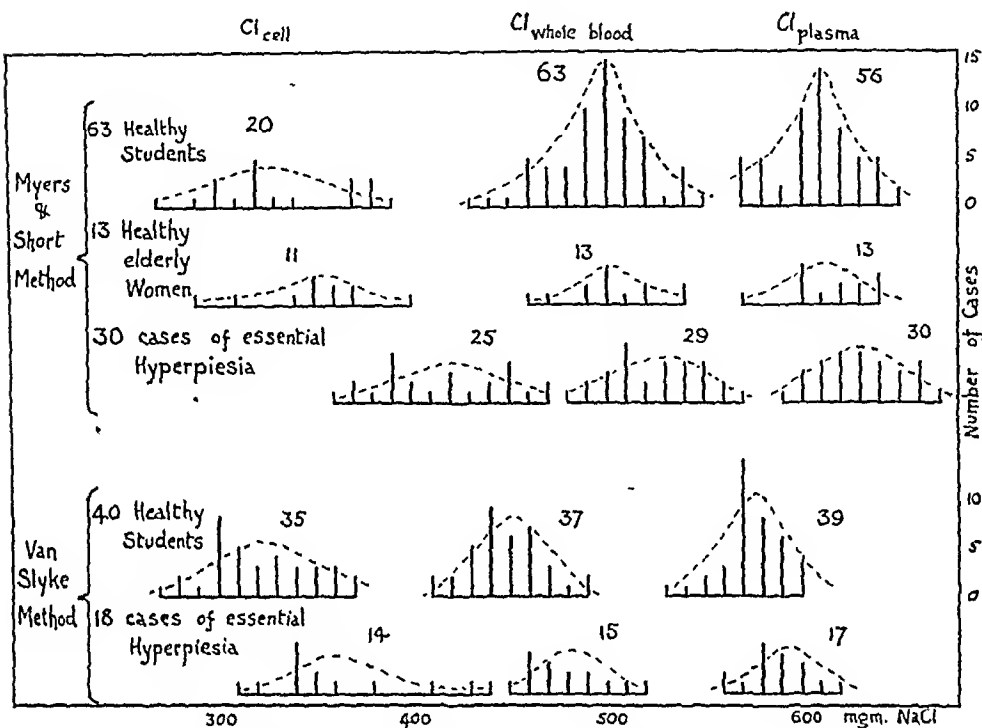


FIG. 1.—The distribution of chlorides in plasma (Cl_p), whole blood, ($Cl_{w.b.}$), and red cells, (Cl_c), in people with normal and with high blood pressure. The abscisse represent the numbers of individuals with the chloride concentrations indicated in the ordinates. The different results given by the two methods of chloride estimation, viz., Myers and Short, and Van Slyke, are also shown. Note the marked rise in red cell chloride in high blood-pressure patients. The figures near each group indicate the number of individuals in that group.

Lest it be objected that the addition of oxalate to the blood might alter the distribution of ions between plasma and red cells, we would point out that Van Slyke^{11a} has shown that, as regards the distribution of CO_2 , practically no alteration takes place, whereas our own experiments showed that the addition of oxalate had no effect on the distribution of chloride (within 1%) compared with that in defibrinated blood.

B. Erythrocyte Volume-index and Blood pH. For this study we used a second group of patients, employing the microtechnique of Shock and Hastings,¹⁰ but with the exception that, instead of using finger-prick blood and oxalate, we drew 3 cc. blood from the median-basilic vein without stasis into an oiled syringe, defibrinated with mercury (Eisenmann method³) and used the blood for hematocrit (3000 r.p.m. for 1 hour) and pH studies.

Blood counts were made by an experienced technician, the average of two counts checking within 0.5% being taken. After counts made on defibrinated blood and on a fraction of blood oxalated according to the method of Heller and Paul⁷ were found to be identical on 10 occasions,

we confined ourselves to the latter method. From the above data the erythrocyte volume-index was calculated by the method of Haden.⁶

Results. Our results show: (Table 1).

TABLE 1.—AVERAGE BLOOD VALUES.

	Normal group.	Hypertension group.
Plasma Cl (as mg. NaCl)	581.0	588.0
Red cell Cl (as mg. NaCl)	328.0	373.0
Plasma CO ₂ (as vol. %)	77.9	73.3
Red cell CO ₂ (as vol. %)	54.0	51.5
Plasma total anions (A) _p (as N solution)	0.1350 N	0.1332 N
Red cell total anions (A) _c	0.0805	0.0870
Ratio $\frac{(Cl)_c}{(Cl)_p}$	0.56	0.63
Ratio $\frac{(CO_2)_c}{(CO_2)_p}$	0.69	0.70
Ratio $\frac{(A)_c}{(A)_p}$	0.60	0.65
Red cell vol. %	49.0	46.7
Blood pH	7.34	7.34
Volume index (red cells)	1.015	1.008

1. The chloride content of the plasma in people with hypertension is practically the same as, or slightly higher than, that in normal people. In red cells, however, the chloride content per 100 cc. is raised considerably, on the average by 14% (Van Slyke's method) and 18% (Myers and Short's method). Fig. 1, however, shows that there is some overlapping of the normal and hypertension groups as regards red cell chloride, *i. e.*, people with high blood pressure do not necessarily have red cell chloride higher than may be found in normal people.

2. The CO₂ capacity of both plasma and red cells falls by a few volumes per cent, though again, as with the chlorides, the normal and hypertension groups overlap.

3. When the results above are calculated as the sum of the chloride and bicarbonate ions and plotted in terms of normality, the plasma values found for our group of normal young people is 0.1350 N (which is identical with that found by Atehley, Loeb, Benedict and Palmer¹), while in our hypertension group the value is slightly less, 0.1332 N.

4. When from these results we calculate the ratio of chloride (or CO₂, or total anions) in the red cells to chloride (or CO₂ or total anions) in the plasma, we find that the ratios in the hypertension group are increased in value.

5. The average red cell volume per 100 cc. blood in our hypertension group was 46.7, a figure usually regarded as normal, though slightly less than that found in our normal student group.

6. There were no significant differences between the normal and hypertension groups as regards blood pH or erythrocyte volume-index. Thus in our normal group the pH and volume-index averages

were 7.34 and 1.015 respectively (with ranges of 7.29 to 7.39 and 0.917 to 1.057 respectively), while in the hypertension group the averages were for pH 7.34 and for volume-index 1.008 (with ranges of 7.28 to 7.50 and 0.849 to 1.160 respectively). (Table 1 and Fig. 2.)

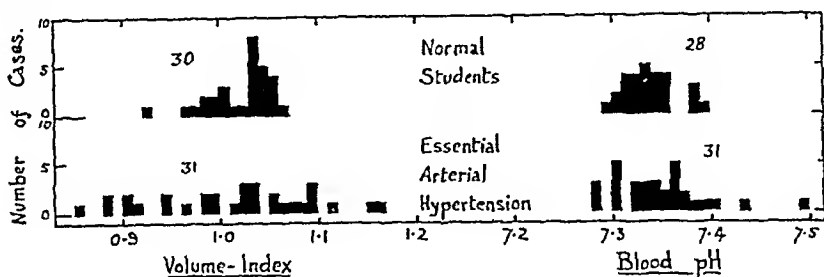


FIG. 2.—A comparison between two groups, (a) 30 normal students, and (b) 31 patients with arterial hypertension, as regards blood pH and volume index of red cells. Abscissæ represent numbers of individuals having the pH and volume index shown.

The Significance of These Results. The laws relating to the distribution of ions have recently been summarized by Van Slyke.^{11c} One is to the effect that the ratio of chloride concentration in the cells to chloride concentration in plasma, is equal to the ratio of the bicarbonate concentration in the cells to the bicarbonate concentration in the plasma, which is in turn equal to the ratio of the concentration of anions in the cell to those in the plasma, and again to the ratio of the hydrogen-ion concentration in the plasma to the hydrogen-ion concentration in the cells. The numerical value of this ratio is determined by the concentration of base-binding hemoglobin in the cell.

This law may be expressed thus:

$$\frac{[Cl']_c}{[Cl']_p} = \frac{[HCO_3']_c}{[HCO_3']_p} = \frac{[A']_c}{[A']_p} = \frac{[H]_p}{[H]_c} = 1 - \frac{[Hb']_c}{2[A']_p} \quad (\text{Formula I})$$

-(The use of the brackets is to indicate concentration of ions)

In actual practice, however, this law is not strictly true. It has been found for instance, in defibrinated horse's blood, on which these laws were first worked out, that actually

$$\frac{[Cl']_c}{[Cl']_p} = 0.81 \frac{[HCO_3']_c}{[HCO_3']_p}$$

Van Slyke and his colleagues have further shown that the values of the ratios in Formula I rise or fall with increasing or diminishing H-ion concentration of the blood. This at once suggested that the rise in the ratio $\frac{[Cl']_c}{[Cl']_p}$ in our hypertension group might be the result of acidemia. This suggestion is supported by the recently published work of Doles² who claims to have found an increase in the volume of the individual erythrocytes (Volume Index) in arterial hyper-

tension, an increase which he asserts is directly proportional to the systolic pressure. Now it is well known that increase of volume index can be brought about by raising the H-ion concentration of blood, when both water and chlorides pass from the plasma into the red cells (Hamburger's phenomenon). Against the acidemia theory, however, was the fact that the ratio $\frac{[\text{HCO}_3']_c}{[\text{HCO}_3']_p}$ was not increased in our hypertension group. Our later studies, showing no change in blood pH and volume index, finally disposed of the acidemia hypothesis.

There are, however, other suggestions which have been put forward to explain the high cell chloride in arterial hypertension. Some of these are now being investigated.

Summary. In a study to determine the site of increased blood chloride in patients with arterial hypertension, and if possible its significance, it was found:

1. The increased blood chloride is wholly confined to the red cells.
2. This increased cell chloride is not the result of acidemia, since pH and erythrocytic volume-index showed no significant deviations from the normal.

REFERENCES.

- (1.) Atchley, D. W., Loeb, R. F., Benedict, E. M., and Palmer, W. W.: *Arch. Int. Med.*, 31, 606, 1923. (2.) Doles, H. M.: *Virginia Med. Monthly*, 62, 489, 1935. (3.) Eisenmann, A. J.: *J. Biol. Chem.*, 71, 607, 1927. (4.) Evans, C. L.: *Recent Advances in Physiology*, London, J. & A. Churchill, 1925, p. 1. (5.) Greenwald, I., and Gross, J.: *J. Biol. Chem.*, 54, 589, 1922. (6.) Haden, R. L.: *J. Lab. and Clin. Med.*, 15, 736, 1930. (7.) Heller, V. G., and Paul, H.: *Ibid.*, 19, 777, 1933-1934. (8.) Myers, V. C., and Short, J. J.: *J. Biol. Chem.*, 44, 47, 1920. (9.) Ponder, E., and Saslow, G.: *J. Physiol.*, 70, 18, 1930. (10.) Shock, N. W., and Hastings, A. B.: *J. Biol. Chem.*, 104, 565, 1934. (11.) Van Slyke, D. D.: (a) *Ibid.*, 30, 347, 1917; (b) 58, 523, 1923-1924; (c) *Factors Affecting the Distribution of Electrolytes, Water and Gases in the Animal Body*, Philadelphia, J. B. Lippincott Company, 1926.

ELECTROCARDIOGRAPHIC CHANGES OCCURRING AT DEATH.

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COMPARATIVELY few electrocardiographic studies of the dying human heart are recorded in the literature. In 1933, Hanson and co-workers⁴ collected 70 cases in which such studies had been made,

and added 25 cases of their own, making a total of 95. No other important additions have been made since then.

Many of the previously reported cases do not contain sufficient detail because the observations were made for very short periods before death. Changes that might have occurred before or after clinical death were therefore missed.

This paper covers electrocardiographic changes occurring at death in a series of 20 cases, in 6 of whom autopsies had been obtained. In many cases tracings were started several hours before expected death and continued from time to time after clinical death occurred. Some had tracings from days or weeks before, for comparison.

The purpose of this report is to add to the data collected by previous writers on the nature and mode of cessation of cardiac activity. It contains certain facts which might be used in the meager beginnings so far made to solve the mystery of life and death.

Case Reports. *CASE 1.*—J. H., female, aged 70, died May 31, 1933. The postmortem findings were pneumococcus meningitis, bilateral bronchopneumonia, and acute tracheobronchitis. The heart weighed 335 gm.; myocardium was brown in color; mitral and aortic valves were slightly thickened; and there was slight shortening of the chordæ tendineæ. The coronary arteries were patent throughout and showed some yellowish intimal patches. Microscopically, there was marked fibrosis of the myocardium.

The electrocardiogram (Fig. II-A) 2 days before death shows a rate of about 122, regular sinus rhythm. Conduction normal. There is left axis deviation. The *P* wave is notched in the first, and diphasic in the third lead. *Q-R-S* slightly slurred in the second and third leads. Twenty-five minutes before death (B) there is nodal rhythm, rate 80. The *Q-R-S* complex is of lower voltage, slurred, *S-T* segment rounded and *T* wave negative. Twenty minutes before death (C) the rate is about 60; *T* wave is diphasic. Fifteen minutes before death (D) the rate is about 58, *S* wave is larger, the *S-T* segment is rounded and depressed and the *T* wave is diphasic. Ten minutes before death (E), there is shortening and slurring of the *R* wave, disappearance of the *S* wave, a high *R-T* take-off with positive *T* wave. There appears to be a wave on the *R-T* segment which might be of auricular origin. Five minutes before death (F) diphasic waves appear at the rate of about 52 per minute, preceded by fine, almost isoelectric vibrations which might be a part of the *Q-R-S* complexes. Three minutes before death (G) ventricular fibrillation appears. Three minutes after clinical death (H) there is cardiac standstill, with an occasional monophasic impulse, which appeared for about 2 minutes.

CASE 2.—R. G., female, aged 43, died January 27, 1936, of lobar pneumonia. On postmortem the heart was found to weigh 250 gm. There were no gross or microscopic abnormalities except for an occasional atherosclerotic plaque in the coronary arteries.

The electrocardiogram at 10.15 A.M., 4 hours before death (Fig. III-A) shows regular sinus rhythm with a rate varying between 117 and 153 per minute. The *R-T* segment in the first and second leads is slightly depressed and rounded and slightly elevated in the third lead. At 2.07 P.M., 2 minutes before death (B), the rate is 75 per minute. The *P* wave is of low voltage in the first lead, negative in the second, and diphasic in the third. The axis is rotated to the left and the *T* waves are of higher voltage. At 2.10

P.M. (C), 1 minute after clinical death, monophasic ventricular waves take the place of the normal complexes and this continued for about 2 minutes, when the heart stopped.

CASE 3.—M. G., female, aged 65, died January 10, 1936. The post-mortem findings were cerebral hemorrhage, bronchopneumonia, diaphragmatic hernia, and general arteriosclerosis. The heart was grossly normal, but microscopically, the myocardial fibers showed marked fragmentation, many brown pigment granules deposited at the poles of the nuclei, marked atherosclerosis of the small coronary branches, with almost complete obliteration of some of the lumina.

An electrocardiogram (Fig. IX-A) obtained at 4.55 P.M., about 9 hours before death, shows regular sinus rhythm, left axis deviation and low voltage *T* waves in all leads. The *Q-R-S* complexes are notched in the second lead. At 11.30 P.M., 2 hours before death (B), *Q-R-S* is of slightly voltage. At 1.40 A.M. (C), 3 minutes after clinical death, and continuing for 10 minutes, an occasional auricular impulse is seen and the ventricular impulses appear independently, at a rate of about 45 per minute. They are of lower voltage and have high *R-T* segments.

CASE 4.—A. D., female, aged 60, died October 17, 1935. The post-mortem findings were cerebral thrombosis, subarachnoid hemorrhage and generalized arteriosclerosis. The heart weighed 310 gm.; mitral, tricuspid and aortic valves were moderately thickened. At the origin of the left descending coronary artery there was marked sclerosis and calcification, the lumen was patent in the proximal 2 cm., but narrowed down to a mere slit lower down. The right branch was patent throughout and there were atheromatous patches present in the intima. The microscopic findings were marked sclerosis of the small coronary branches with fibrosis of the myocardium.

The electrocardiogram (Fig. X) for a period of 1 hour after clinical death showed an occasional interruption of cardiac standstill by a supraventricular impulse.

CASE 5.—D. S., male, aged 58, was admitted on several occasions because of hematemesis. He died December 20, 1935, after a massive hemorrhage. The postmortem findings were hepatic lobatum, esophageal varices, splenomegaly with thrombosis of the splenic vein. The heart weighed 300 gm. The wall of the right ventricle was 0.5 cm. thick, left ventricle 1.5 cm. The mitral valve was moderately thickened; the aorta showed marked tree barking. Microscopically, there was diffuse fibrosis of the myocardium and some brown atrophy.

The electrocardiogram (Fig. XVI-A) obtained 35 minutes before death, with patient unconscious and pulse hardly perceptible, shows regular sinus rhythm, rate about 129. The conduction time is normal. Five minutes before death (B), the complexes are of lower voltage. After clinical death (C), marked sinus bradycardia is noted with an occasional auricular premature contraction. The rate is variable, being at times as low as 15 per minute. The *P-R* conduction time is shortened from the previous 0.14 seconds to 0.10 seconds. There is thickening and widening of the *S* wave.

CASE 6.—P. P., a female, aged 36, admitted January 24, 1936, and died within a few hours after admission. The postmortem findings were generalized arteriosclerosis, and massive cerebral hemorrhage. The heart weighed 450 gm., the apex was blunt. The auricles were thin-walled; valves normal; the right ventricle measured 0.5 cm. in thickness with flattening of the musculi carnei; the left ventricle measured 2 cm. in thickness, the musculature being slightly flattened. The coronary arteries showed minimal atheromatosis. Microscopically, there was diffuse fibrosis of the myocardium with brown atrophy and some fragmentation.

An electrocardiogram (Fig. XVII) obtained 10 minutes before death

shows marked sinus bradycardia and arrhythmia, with a rate varying between 25 and 63. The *P-R* conduction time is 0.14 to 0.18 seconds and the *Q-R-S* interval time is 0.08 seconds. There is a tendency towards right axis deviation with diphasic *T* waves arising abruptly from the *Q-R-S* complexes.

TABLE 1.—SUMMARY OF THE OTHER 14 CASES.

Case.	Sex.	Age.	Diagnosis.	Progressive electrocardiographic changes.
7 (Fig. 1)	F	16	Acute peritonitis following operation for chronic appendicitis	(A) Right axis deviation, nodal rhythm; (B) frequent ectopic ventricular impulses; (C) only ectopic impulses seen, <i>T</i> waves of lower amplitude; (D) changing of impulse focus; triphasic <i>T</i> waves; cardiac standstill followed.
8 (Fig. 4)	M	59	Atrophic cirrhosis of liver	(A) Regular sinus rhythm, left axis deviation; (B) lower voltage complexes; (C) auricular activity disappears; (D) multi-foci ventricular complexes; transient ventricular fibrillation (C, D)
9 (Fig. 5)	M	19	Lobar pneumonia, Type II	(A) Regular sinus rhythm, rate 144; (B) complete <i>A-V</i> dissociation, supraventricular and ectopic ventricular complexes; (C) cardiac standstill for 30 seconds; (D) nodal premature contractions, occasional auricular and ventricular ectopic impulses; (E) cardiac standstill, occasional ectopic ventricular impulse.
10 (Fig. 6)	F	40	Metastatic malignancy with possible metastasis to heart	(A) Regular sinus rhythm, rate 156, <i>Q-R-S</i> low voltage, notched; (B) sinus arrhythmia, rate 57, changing <i>Q-R-S</i> ; (C) occasional auricular impulse, supraventricular impulses, rate 33, higher voltage, rate 27; (D) low voltage complexes, slurred, no <i>P</i> waves.
11 (Fig. 7)	M	44	Postoperative thyroid crisis	Complete cardiac standstill, interrupted occasionally by multifocal ectopic ventricular impulses.
12 (Fig. 8)	M	59	Coronary thrombosis	(A) Transient ventricular fibrillation, cardiac standstill, ectopic supraventricular impulses, sinus rhythm, <i>R-T</i> segment elevated and notched; (B) prolonged cardiac standstill, ectopic impulses resembling ventricular fibrillation.
13 (Fig. 11)	M	65	Bleeding gastric ulcer	(A) Regular sinus rhythm, right axis deviation, low voltage <i>Q-R-S</i> ; (B) axis shift to left, low <i>T</i> wave; (C) rate 41, <i>P-R</i> 0.4 seconds, left axis deviation, diphasic <i>T</i> wave, prolonged <i>S-T</i> segment.
14 (Fig. 12)	F	26	Ruptured ectopic pregnancy	(A) Pre-operatively-regular sinus rhythm; (B) <i>R</i> wave higher, slurred, <i>S-T</i> depressed; (C) <i>Q-R-S</i> higher, well developed <i>S</i> wave; (D) <i>S</i> wave notched; (E) complete <i>A-V</i> dissociation, auricular rate 50, ventricular 24-28; (F) sinus bradycardia, ventricular premature contractions; (G) coarse ventricular fibrillation, short periods ventricular standstill.

TABLE 1.—SUMMARY OF THE OTHER 14 CASES—*Continued.*

Case.	Sex.	Age.	Diagnosis.	Progressive electrocardiographic changes.
15 (Fig. 13)	F	39	Mitral lesion, transient auricular fibrillation. Cerebral embolus	(A) Auricular fibrillation, ventricular rate 180, right axis deviation; (B) ventricular rate 136-158, intraventricular conduction time prolonged to 0.13 seconds; (C) bizarre ventricular complexes, 50-70 per minute.
16 (Fig. 14)	M	60	Cerebral thrombosis; hypostatic pneumonia	(A) Regular sinus rhythm, <i>Q-R-S</i> low voltage, slurred, left axis deviation, <i>Q</i> III; (B) intraventricular conduction time 0.12 second; (C) sinus arrhythmia, <i>Q-R-S</i> increased in amplitude, <i>S</i> III
17 (Fig. 15)	F	69	Cerebral hemorrhage	(A) regular sinus rhythm, left bundle branch block; (B) complete <i>A-V</i> dissociation; (C) auricular activity has ceased; (D) cardiac standstill interrupted by ventricular prematurity, progressive changes in <i>T</i> wave; (D and E).
18 (Fig. 18)	M	23	Rheumatic, mitral, and aortic lesions; auricular fibrillation; decompensation.	Complete cardiac standstill, interrupted by short periods of ventricular fibrillation.
19 (Fig. 19)	M	32	Rheumatic, mitral, and aortic lesions; auricular fibrillation, congestive failure	(A) Auricular fibrillation, ventricular rate 120; (B) rate 32, <i>Q-R-S</i> changed; (C) delayed intraventricular conduction time; (D) occasional bigeminal rhythm; (E, F) slowed ventricular rate; (G, H, I, J) progressive changes in the complexes; (K) cardiac standstill interrupted by premature contraction.
20 (Fig. 20)	M	38	Attacks of syncope, convulsions; diagnosis not established	Fine ventricular fibrillation, interrupted by periods of multifocal ventricular paroxysmal tachycardia.

SUMMARY OF THE ELECTROCARDIOGRAPHIC CHANGES. Due to the great variety and rapidly shifting nature of the electrocardiographic changes, only the gross findings may be summarized. In the early records, 8 cases presented sinus tachycardia and 2 auricular fibrillation. The latter existed for many days before and cannot be considered one of the changes occurring in the process of death. This corroborates the findings of Willius,¹⁴ Hanson and his coworkers,⁴ Kahn and Goldstein⁸ and Robinson.¹¹ Carter² claims that this disturbance does occur as a death phenomenon, but does not give any case reports.

Progressive sinus slowing occurred in 8 cases. Sinoauricular standstill followed. Ectopic impulses assumed the leadership of cardiac activity in many cases. Six developed nodal rhythm, 3 a single-focus ectopic ventricular rhythm, and several, multifocal ventricular impulses. In all these, the impulses produced a ventricular bradycardia at the same time that the auricles were either at a standstill or showed only occasional activity. In 1 case, there was a return from nodal rhythm and bradycardia to sinus bradycardia

and back again. Two showed an occasional return of auricular activity. Two others developed changes in the configuration of the *P* wave, with its ultimate disappearance. Two cases developed partial, and 3 complete auriculoventricular block. In Hanson's series, 7 cases out of 25, and in Willius', 4 out of 6, showed auriculoventricular block in various degrees. Two developed marked sinus arrhythmia. There were no instances of auricular flutter, although Willius claims to have observed 1 case in his series. Eight showed

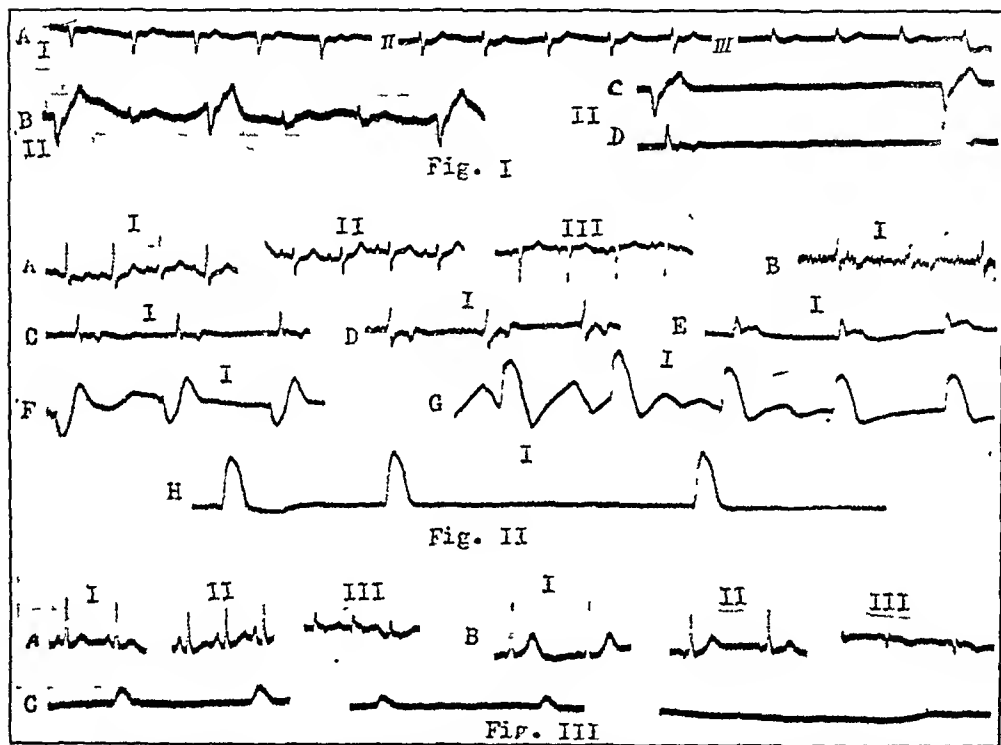


FIG. 1.—(Case 7.) A, three standard leads 10 minutes before death; B and C, the second lead 5 and 1 minute before death, respectively; D, immediately after clinical death.

FIG. 2.—A, 2 days before death; B, C, D, E, F and G, Lead I, 25, 20, 15, 10, 5 and 3 minutes before death, respectively; H, 3 minutes after clinical death.

FIG. 3.—A, 4 hours before; B, 3 minutes before and, C, 1 minute after clinical death.

complete cardiac standstill for variable periods, interrupted from time to time by ectopic ventricular impulses in 3, by ventricular fibrillation in 3, and by multifocal impulses with periods of ventricular paroxysmal tachycardia in 1 case.

Of intraventricular disturbances may be mentioned gradual changes in the *Q-R-S* complexes in 9 cases: diminished voltage in some, increased voltage in others, shifting of the electrical axis from right to left, shortening and marked widening with slurring and notching of the *S* wave or increased voltage of the *S* wave. Marked

progressive changes in the *R-T* and *S-T* components occurred in 6 cases. These consisted of rounding, depression, elevation, very high takeoff, prolongation, notching, shortening, widening and thickening. In 7 cases the *T* component also underwent definite changes, becoming isoelectric, diphasic, changing from a negative to a positive phase, increase in voltage, or taking an abrupt rise from the *Q-R-S* component.

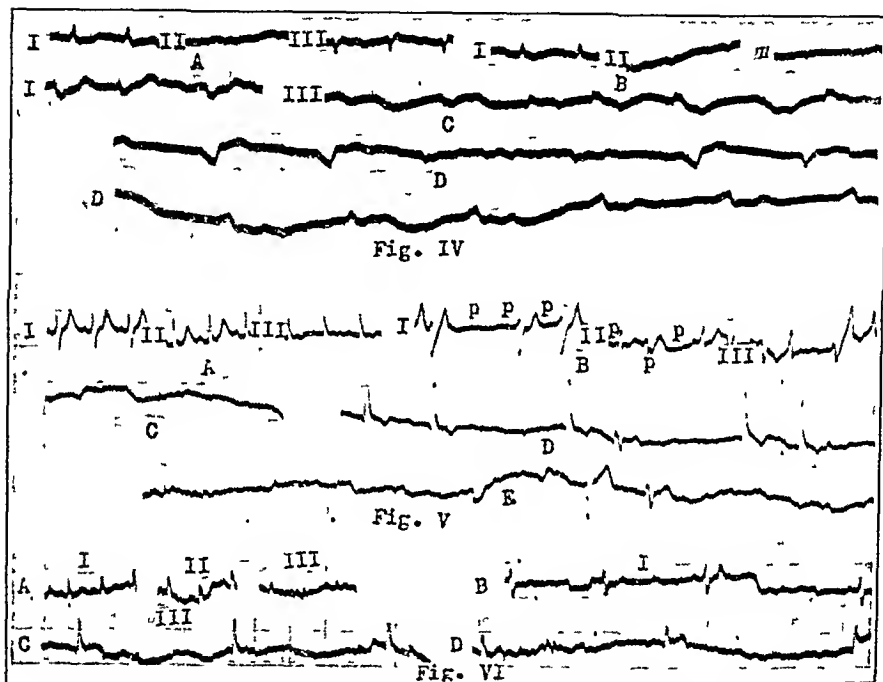


FIG. 4.—(Case 8.) A, three leads, 90 minutes before death; B, three leads, 40 minutes before death; C, Leads I and III, 5 minutes before death; D, Leads I and III, immediately after death.

FIG. 5.—(Case 9.) A, three leads, several hours before death; B, three leads, 15 minutes before death; C, cardiac standstill, lasting 30 seconds, 10 minutes before death; D, soon after standstill; E, after clinical death.

FIG. 6.—(Case 10.) A, B and C, 45, 15 and 5 minutes before death, respectively; D, after patient stopped breathing.

Four cases showed a rapid development of bundle branch block. In 7 cases, ventricular fibrillation occurred, either as a terminal event or for very short periods, interrupted by cardiac standstill or other disturbances. Hanson found this disturbance in 10 of 25, Willins in 4 of 6, and Kahn in 2 of 7 cases. In Turner's series¹³ the incidence was 20% in 45 cases collected from the literature.

In several of our cases electrocardiographic changes occurred as long as 1 hour after clinical death. Similar observations were made by Turner,¹³ Hoesslin,⁷ Robinson,¹¹ Hassenfeld⁵ and in experimental

animals by Bruns.¹ There were ectopic ventricular contractions, monophasic impulses, an occasional auricular or supraventricular impulse, bizarre complexes and sinus bradycardia. Ventricular fibrillation at times superseded the above.

Discussion. In times past there was a question of what part of the heart stops beating first at death. Koch⁹ believed that the region of the coronary sinus, and Hering⁶ that the sino-auricular node, was the last to die. G. C. Robinson showed that there was no constant area in the human heart that dies last.

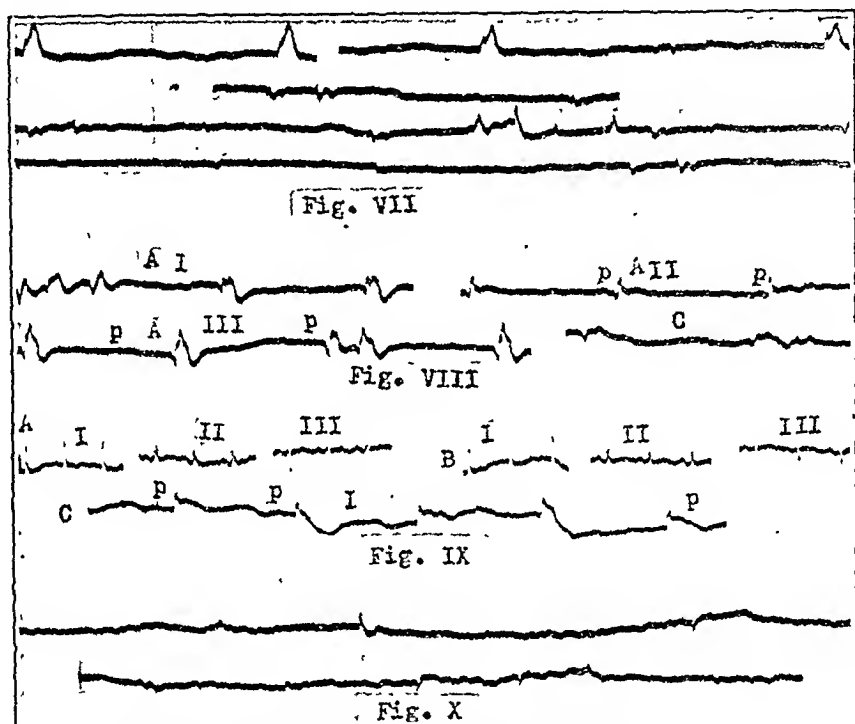


FIG. 7.—(Case 11.) Five to 15 minutes after clinical death.

FIG. 8.—(Case 12.) A, three leads, 2 minutes before death; B, Lead I, 10 minutes after death.

FIG. 9.—A, three leads, 9 hours before death; B, three leads, 2 hours before death; C, Lead I, 10 minutes after death.

FIG. 10.—One hour after death.

That contraction of the heart takes place concomitantly with electrical phenomena was established experimentally by Einthoven and Hugenholtz,³ who contradicted the statement of Mines and Noyons¹⁰ that electrical manifestations are recorded experimentally long after muscular contraction can be recorded. Einthoven and Hugenholtz showed this to be due to the use of an insensitive apparatus for registering mechanical beats.

Appreciation of this fact is valuable in interpreting the significance of the electrocardiographic manifestations before and after death. Hasensfeld's idea that electrocardiographic changes after clinical

death are caused by "possibility of hidden life" and that contraction of the heart is not the only cause of electrocardiographic phenomena requires elucidation and proof. There is one concrete factor besides contraction that may be associated with electrocardiographic manifestations, and that is "the current of injury." This factor might play some part in producing some of the bizarre, monophasic waves.

This study confirms the belief that death of the entire body or even special organs does not occur simultaneously. After clinical

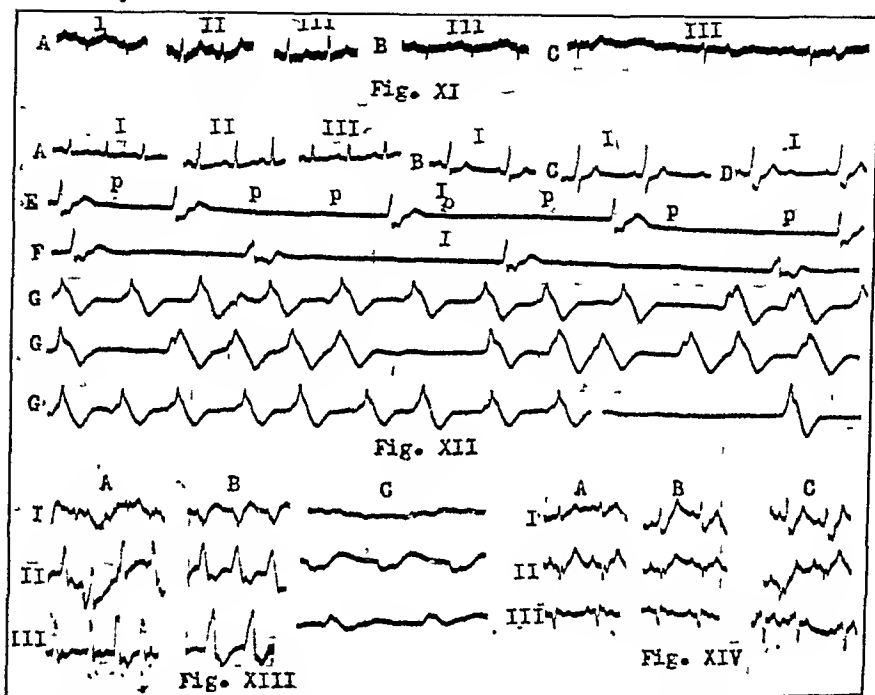


FIG. 11.—(Case 13.) A, three leads, 2 hours before death; B, Lead III, 45 minutes before death; C, Lead III, on death.

FIG. 12.—(Case 14.) A, three leads, 2 hours before death; B, C, D, E, F and G, Lead I, 30, 25, 20, 15, 5 and 2 minutes before death, respectively.

FIG. 13.—(Case 15.) A, three leads, 30 minutes before death; B, 5 minutes before death; C, on death.

FIG. 14.—(Case 16.) A, B and C, 1 hour, $\frac{1}{2}$ hour and 2 minutes before death, respectively.

death, some organs or portions of organs continue to live. This was corroborated by Dr. Charles Norris who was quoted as having observed rare instances of auricular contraction 18 hours after accidental death, with the body kept on ice for that period.

There are many factors operative in bringing about the rapid alterations in the electromotive, and therefore contractile, forces and ultimate stoppage of the heart. Of these may be mentioned changes in the vagosympathetic control of the heart; anoxemia and

carbon dioxide accumulation in the body due to failure of the respiratory center; changes in the hydrogen-ion concentration of the blood; toxic factors; and nutritional disturbances. That anatomic disease of the heart itself is not the cause of the manifestations is evidenced from our observations that the electrocardiographic disturbances at death among those who showed conspicuous anatomic heart disease, postmortem or antemortem, were the same as in those who had anatomically normal hearts. Furthermore, there

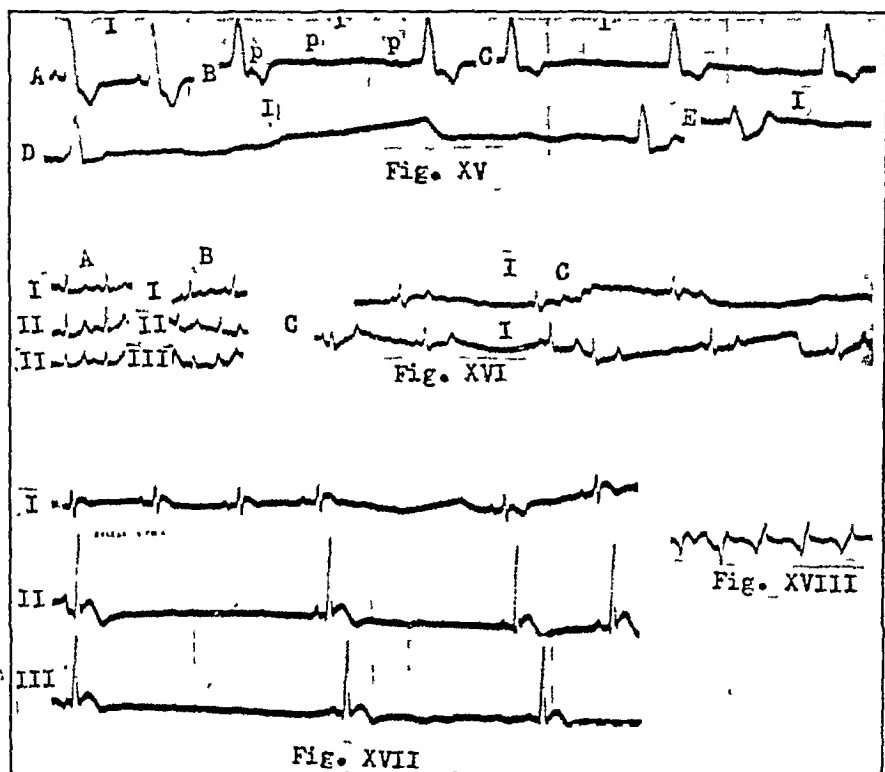


FIG. 15.—(Case 17.) Lead I. A, B, C and D, 15, 8, 4 and 2 minutes before death, respectively.

FIG. 16.—A and B, three leads, 35 and 5 minutes before death, respectively; C, Lead I, 10 minutes after death.

FIG. 17.—Three leads, 10 minutes before death.

FIG. 18.—(Case 18.) Small part of tracing 1 hour after death.

were no acute anatomic changes in the heart noted on postmortem examination that may be considered to have been produced immediately before death. The lesions found were of an older nature.

About half of our cases showed marked sinus acceleration of the heart early, due to excessive sympathetic nerve irritability. As time went on, sympathetic control was gradually lost and a vagotonic state developed, resulting in marked sinus slowing and final sino-auricular standstill in some, and auriculoventricular block in others. These manifestations were similar to those produced by the

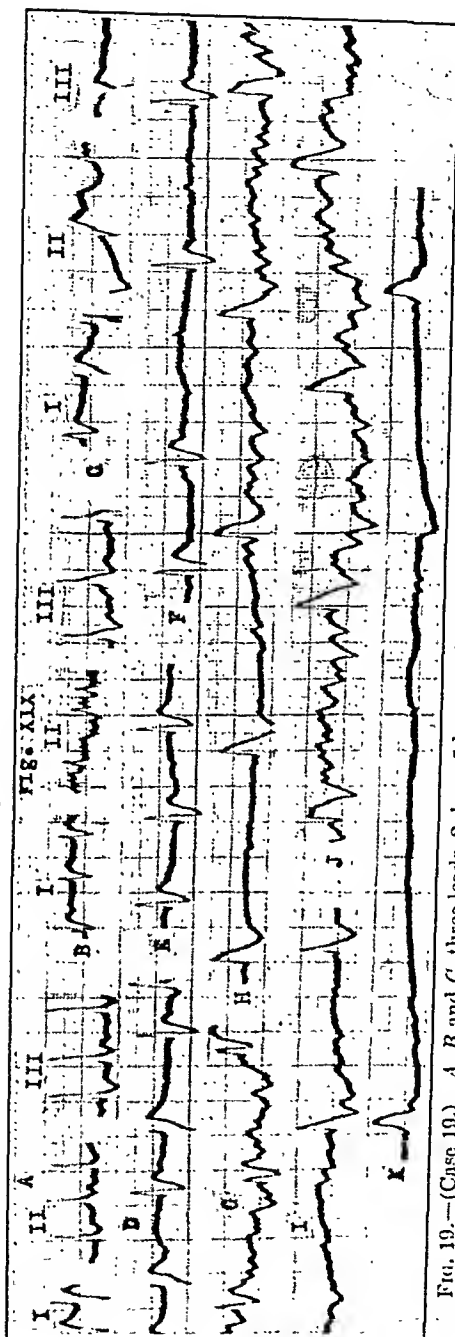


FIG. 19.—(Case 19.) A, B and C, three leads, 2 days, 5 hours and 2 hours before death, respectively; D, E, F, G, H, I and J, Lead I, 45, 40, 35, 30, 10, 5 and 3 minutes before death, respectively; K, Lead I, soon after death.

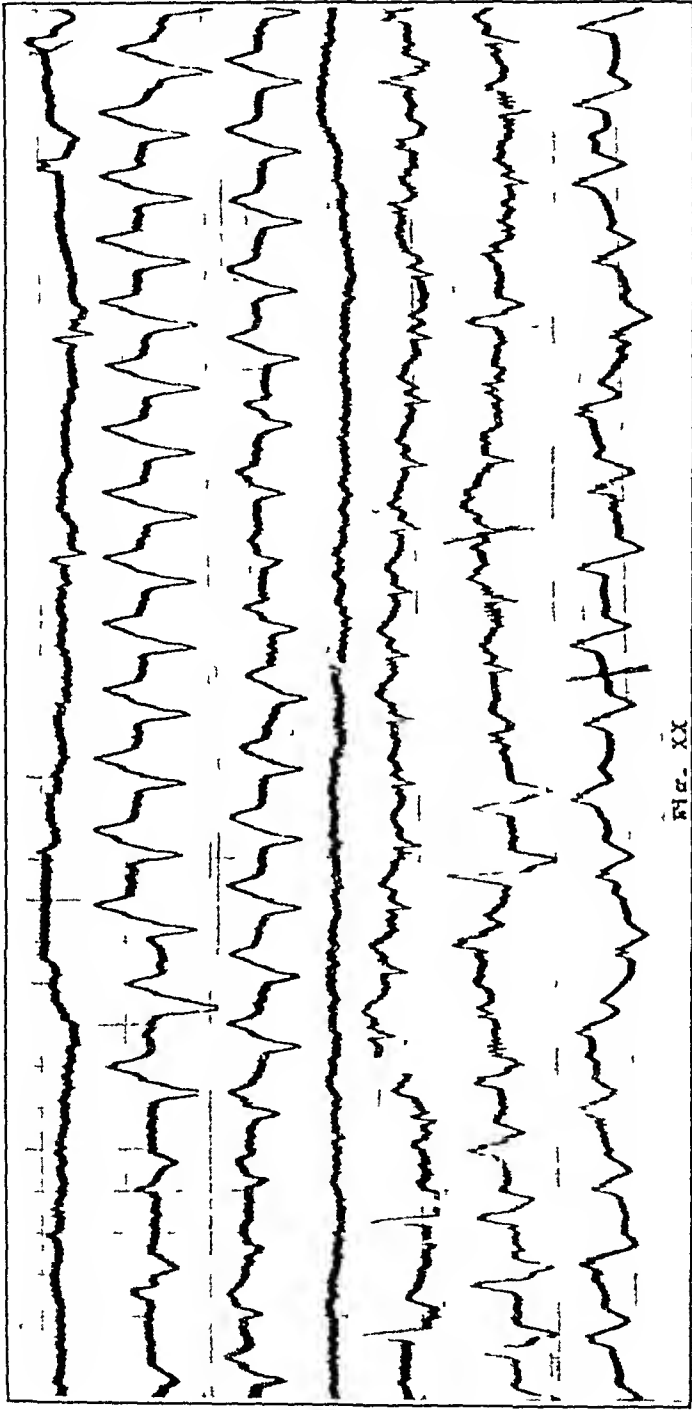


Fig. 20 — (Case 20) Various phases observed within 1 hour before death.

carotid sinus reflex previously described by Sigler.¹² Marked sinus arrhythmia observed in 2 cases is further proof of vagotonia. The sinus slowing and standstill may partly be due to local anoxemia to which the sinoauricular node is particularly susceptible.

Marked vagal slowing or stoppage of the heart necessarily results in circulatory insufficiency and failure, aside from the vasomotor and respiratory failure present at these stages. Nutritional disturbances and anoxemia of the heart itself result in further changes in the electrical conductivity and mechanical contractility. This is shown in the changes of the initial as well as the terminal ventricular complexes from time to time. They depict gradual changes in the distribution of the excitation wave in the ventricular wall and the order of excitation and retraction. Transient focal blocking develops in various parts, increasing in degree to a point of bundle branch block. Local points of irritability in various areas in the ventricles and, at times, also in the auricles develop, resulting in aberrant impulses with uneven spread, either because of partial or total refractoriness in certain areas or focal changes in ionic composition and nutritional state of the muscle. Convulsive movements and localized tremors of the heart finally result, and are shown by ventricular fibrillation and other series of peculiar complexes.

Summary. Electrocardiographic studies were made on 20 cases before, during and after clinical death. The changes noted were: sinus tachycardia, followed by sinus bradycardia and sinoauricular standstill; development of ectopic foci of irritability, resulting in nodal rhythm, single- and multifocal ventricular premature contractions and ventricular paroxysmal tachycardia; appearance and disappearance of auricular activity; auriculoventricular block in various degrees; ventricular fibrillation; marked changes in the initial and terminal ventricular complexes; intraventricular conduction disturbances in various degrees up to bundle branch block. In many cases the electrocardiographic manifestations were noted as long as 1 hour after clinical death.

The factors responsible for these electrocardiographic changes appear to be disturbances in the vagosympathetic control of the heart, anoxemia, toxemia and local nutritional and ionic disturbances in the heart. That anatomic disease of the heart itself is not responsible for the ultimate manifestations is evidenced from the fact that these changes occurred in the normal as well as in the diseased hearts. The sinus slowing and standstill, as well as the various grades of auriculoventricular block, appear to be mainly of vagal origin. Intraventricular disturbances are dependent on the other factors. The latter disturbances depict changes in the distribution of the excitation waves and the order of excitation and retraction as well as transient focal blocking and localized partial or total refractoriness.

REFERENCES.

- (1.) Bruns, O.: München. med. Wehnsehr., 81, 1225, 1934. (2.) Carter, J. B.: J. Am. Med. Assn., 99, 1508, 1932. (3.) Einthoven, W., and Hugenholtz, F. W. N.: Nederl. Tijdschr. v. Geneesk., 1, 310, 1919. (4.) Hanson, J. F., Purks, W. K., and Anderson, R. G.: Arch. Int. Med., 51, 965, 1933. (5.) Hasenfeld, A.: J. Am. Med. Assn., 98, 2005, 1932. (6.) Hering, H. E.: München. med. Wehnsehr., 56, 845, 1907. (7.) v. Hoesslin: Berlin Letter, J. Am. Med. Assn., 96, 786, 1931. (8.) Kahn, M. H., and Goldstein, I.: AM. J. MED. SCI., 168, 388, 1924. (9.) Koch, W.: Beitr. z. path. Anat. u. z. allg. Path., 42, 202, 1907. (10.) Mines and Noyons: Quoted by Einthoven and Hugenholtz, Rev. 3. (11.) Robinson, G. C.: J. Exp. Med., 16, 291, 1912. (12.) Sigler, L. H.: Am. Heart J., 9, 782, 1934. (13.) Turner, K. B.: Ibid., 6, 742, 1930-1931. (14.) Willius, F. A.: Med. J. and Rec., 119, 49, 1924.

SYPHILIS OF THE INTERVENTRICULAR SEPTUM AND VENTRICULAR TACHYCARDIA.

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THE following concerns a case of proven syphilis of the interventricular septum with subsequent ventricular tachycardia, which is unique, as far as we know, in medical literature.

Case Report. A sailor, aged 35, was admitted to the British Hospital at Buenos Aires on April 13, 1936, under the medical care of Dr. G. Beyrue, in a state of weakness and general prostration which began suddenly 10 days before admission, while on board ship. On admission, he was complaining of vague pains in his chest and nausea followed by vomiting. The most important affliction he had had was rheumatic fever at 21, from which he recovered without involvement of the heart.

Physical examination showed his general condition to be satisfactory. Axillary temperature: 36.8° C., respiration, 24 per minute; pulse irregular, the rate ranging between 170 and 180 per minute. Blood pressure: 100/85 Hg mm. The apex beat was felt in the sixth intercostal space, in the mid-clavicular line. Both heart sounds were weak. There were no signs of congestive failure.

The intern diagnosed the case as paroxysmal tachycardia and prescribed intravenous digalena, digitalis per os, and in the evenings camphorated oil and sedol.

On the following day the patient's condition was the same, pulse rate being unchanged. Teleradiogram showed a much enlarged heart and congestion of the hilum of each lung. Electrocardiograms showed marked tachycardia of the ventricular rhythm. The curves are fairly typical of ventricular tachycardia (Fig. 1).

Two days later no improvement was noticed with digitalis and quinidine was given by mouth. On listening to the heart a peculiar "to and fro" murmur was heard at the apex. After that, signs of congestive failure developed as evidenced by congestion of both bases, tender and enlarged

liver, cyanosis and edema. White cell count was 23,000 per c.mm. The patient died suddenly during an attack of coughing and dyspnea on April 27, 1936.

Postmortem. Weight of heart 540 gm. Apex round in shape and formed by the left ventricle. Pericardium normal. Both coronary arteries (mouth, trunk and principal branches) were normal, except the left one which, in the zone of the interventricular septum, showed a series of whitish granulations following each other like beads of a rosary. The endocardium was normal. Auriculoventricular and pulmonary valves were normal. Aortic valves were slightly thickened. Myocardium was normal with the exception of the interventricular septum which, in the middle third sector, showed a whitish band stretching from one side of the septum to the other; it was distinct on the right side where it extended as far as the posterior wall of the right ventricle. In the aorta could be noticed small whitish slightly prominent zones vertically arranged and the size of a pin-head or larger.

The histologic examination of the zones in the septum showed a striking infiltration of mononuclears. Lymphocytes and plasma cells surrounded the vessels either irregularly or in masses (Hutinel's microscopic gumma); but sometimes they were not adjacent to vessels (Darier's miliary gumma). There was also granulation tissue in the form of neutrophil-fibroblast infiltration with abundant newly formed vessels (Fig. 2).

Endarteritis obliterans appeared in the small arteries and pericardoneuritis was also observed in the nerves of that zone (Fig. 3). Some of the myocardial fibers were in fragments and some were compressed by granulation tissue. The right branch of His' bundle was destroyed completely by granulation tissue. A mild degree of white cell infiltration in certain zones was the only abnormality observed in the left branch which could be perfectly identified.

The ascending aorta showed cellular infiltration of the adventitia and endarteritis obliterans of the vasa vasorum, cellular proliferation of the elastic coat and parts of fatty degeneration in the internal coat.

Spirocheta pallida were occasionally observed (Dieterle Robert's silver impregnation technique) surrounding the lymphatic nodules, the septum and the vasa vasorum of the aorta (Fig. 4). They had 3 or 4 spirals, except one, which showed 7 spirals and was thickened and retracted with granular ends.

Discussion. Syphilitic lesions of the ascending aorta and mouths of the coronary arteries are common, but adult myocardial syphilis is exceptional and, according to Levine,⁵ has little practical importance. Usually, myocardial syphilis is located in the upper zone of the interventricular septum where the auriculoventricular bundle is located; therefore it was assumed for a long time that complete heart block in the adult was usually caused by a luetic lesion in this area. This hypothesis has proved to be incorrect, the most frequent cause being sclerosis of the septum, coronary disturbance, and exceptionally lues (Gallavardin⁴).

Nowadays, certain conditions are required to prove that myocardial lesions are caused by syphilis. It is not enough to find a zone of sclerosis in the septum. The zone must have all the characteristics of a gumma or sclerogumma in which Schaudinn's spirochete must be found (Warthin⁹).

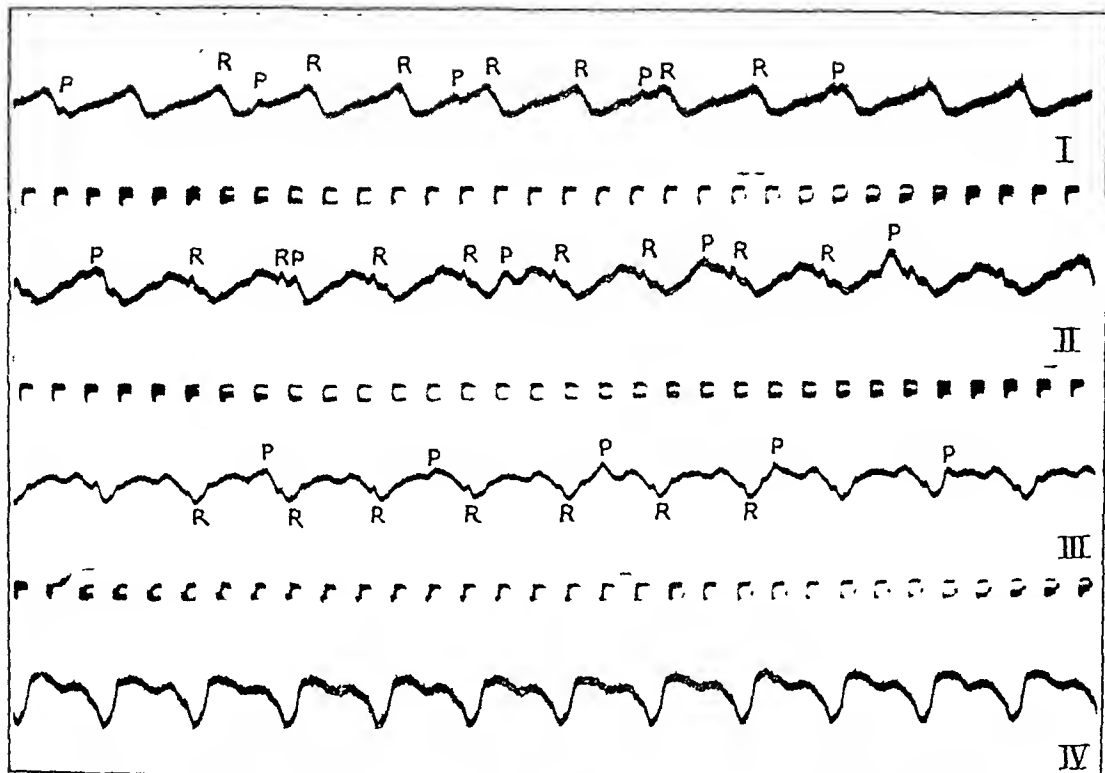


FIG. 1.—Electrocardiogram showing ventricular tachycardia resembling ventricular flutter in Leads I, II and III, but typical in Lead IV.

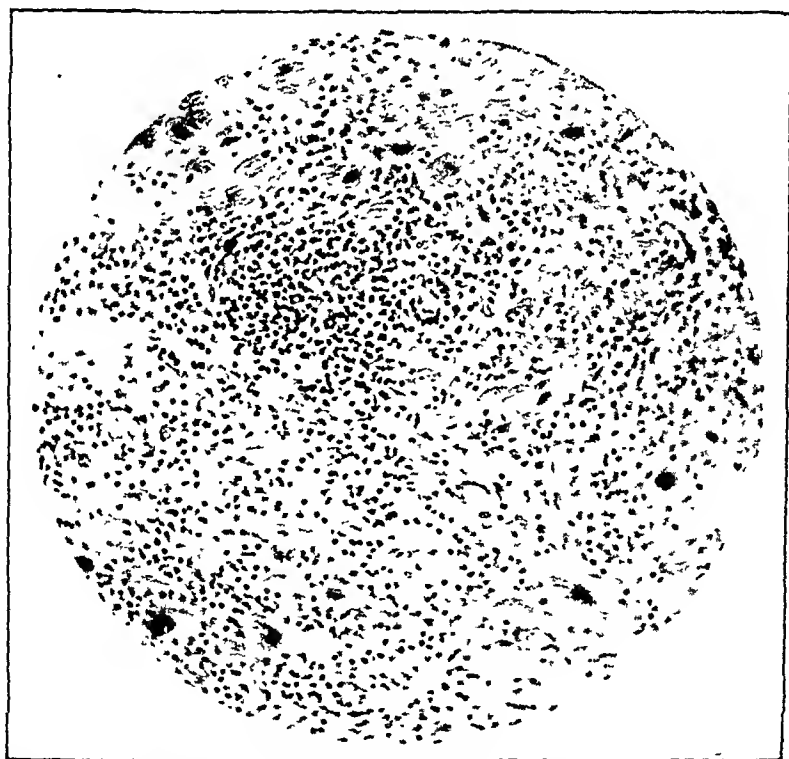


FIG. 2.—Myocardial mononuclear infiltration of the interventricular septum.

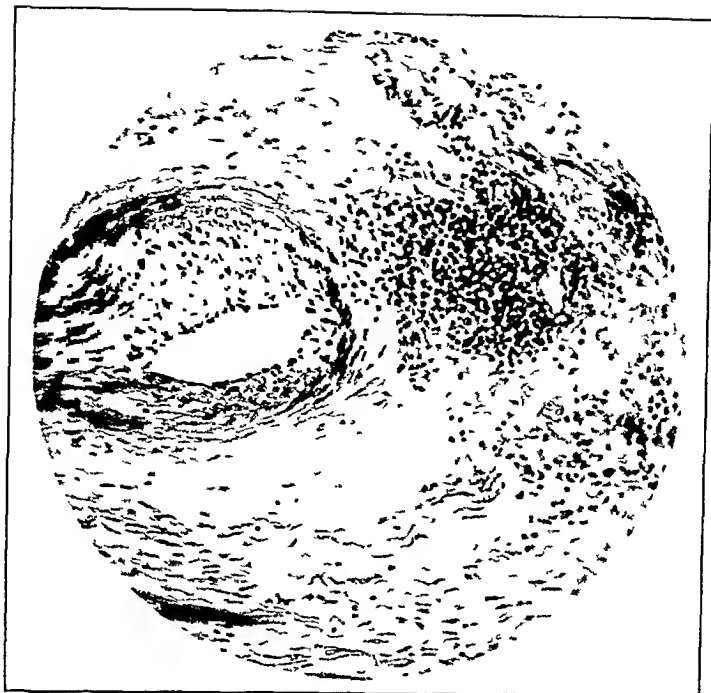


FIG 3—Endocarditis and perivascular infiltration. (Darier's microscopic gumma)

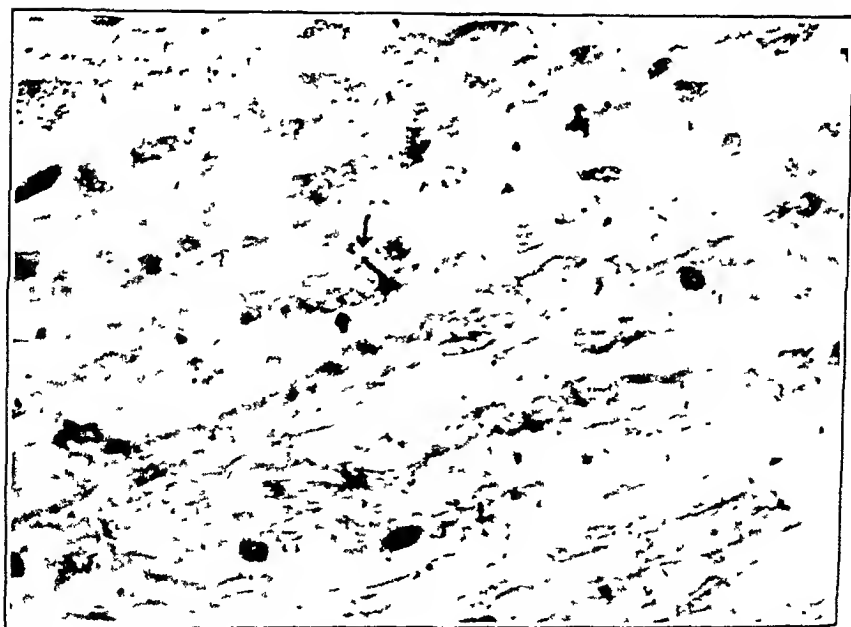


FIG 4.—Microscopic preparation of the interventricular septum showing one spirocheta with seven spirals (arrow).

Our observations fulfill these requirements, because there was a typical sclerogummatous lesion with a typical endocoronaritis and spirochetæ were found in the lesion. Most authors assume that syphilis of the interventricular septum gives rise to an auriculo-ventricular block; however, in our case there was an attack of ventricular tachycardia starting suddenly with nausea, vomiting, precordial aching, low blood pressure, leukocytosis and precordial frictions. These symptoms led us to the diagnosis of infarction of the interventricular septum when the patient was alive (Padilla and Cossio,⁷ Cossio and Bereonsky,² and Cossio.^{1b})

Although the Wassermann test was positive, syphilis was not suspected as the cause, on account of the attack of ventricular tachycardia. Because most authors (Froment³ and Mahaim⁶) do not mention syphilis as a cause of ventricular tachycardia, we thought that this case might have been a juvenile coronaritis (Pezzi⁸) of non-syphilitic origin.

According to our ideas (Cossio^{1a}) and in view of the fact that the patient had a positive Wassermann test, we now believe he had syphilitic aortitis with an infarction of the septum caused by coronary thrombosis of syphilitic etiology.

Summary. 1. This report deals with a case of ventricular tachycardia caused by a syphilitic lesion of the interventricular septum.

2. It was a typical attack of ventricular tachycardia due to infarction of the interventricular septum.

3. The lesion was of the sclerogummatous type with endocoronaritis, and *Treponema pallidum* was found in it.

4. This observation, as far as we know, is the first of its kind in medical literature, and shows that a syphilitic lesion of the septum is able to produce an attack of ventricular tachycardia. In a case of prolonged attack of ventricular tachycardia, provided that the Wassermann and Kahn tests are positive, we must not only suspect infarction of the septum of the ordinary type, but also one of syphilitic etiology.

We are greatly indebted to Dr. G. Beyrre for allowing the publication of this case, and to Dr. S. A. Levine for his suggestions.

REFERENCES.

- (1.) Cossio, P.: (a) Aortitis sífilítica, ed. El Ateneo, Buenos Aires, 1932; (b) *La Semana méd.*, 1, 332, 1933. - (2.) Cossio, P., and Berconsky, I.: *Ibid.*, 1, 884, 1932.
- (3.) Froment, R.: *Les tachycardies paroxystiques ventriculaires*, ed. Masson et Cie, Paris, 1932. (4.) Gallavardin, L.: *J. méd. de Lyon*, 30, 543, 1922. (5.) Levine, S.: *Clinical Heart Diseases*, Philadelphia, W. B. Saunders Company, 1936. (6.) Mahaim, I.: *Les maladies organiques du faisceau de His* Tawara, Paris, Masson et Cie, 1931. (7.) Padilla, T., and Cossio, P.: *La Semana méd.*, 2, 813, 1929. (8.) Pezzi, C.: *Cuore e Circolazione*, 17, 2, 1933. (9.) Warthin, A. S.: *Am. Heart J.*, 1, 1, 1925.

MAINTENANCE OF THE FUNCTIONAL INTEGRITY OF OCCLUDED LARGE ARTERIES AS DEMONSTRATED BY THORO- TRAST ARTERIOGRAPHY.

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IN an article entitled "How Arteries Compensate for Occlusion," E. V. Allen¹ discussed various methods by which a collateral circulation may be established. His statements were the result of extensive experience with thorotrast arteriography, especially of the upper extremities. He noted how a collateral vessel may originate from a small artery above an occluded segment and pass down to empty into the same artery to maintain its integrity. He observed also how lateral branches from one artery may anastomose with an artery of similar size to compensate for occlusion. He indicated how the branches of one vessel could spread out to nourish the territory of neighboring occluded vessels; and he demonstrated the extensive network of very fine vessels which appears in the tissues when the main vessels are obliterated. Inasmuch, however, as Allen's illustrations all concern the arterial tree of the forearm and hand and comparatively small arteries, I should like to make some observations relative to the maintenance or reestablishment of the fundamental integrity of large arteries of the lower extremity which have been occluded. This can perhaps best be done by describing 3 illustrative cases.

Incidentally, for the benefit of those unfamiliar with the subject or technique of arteriography, it may be mentioned that articles of Allen and Camp,² Veal and McFetridge³ and Yater⁴ may be referred to.

Case Reports. CASE 1.—*Clinical History.* A. D., a white man, aged 50, suffered a serious compound fracture of both bones of the left leg in the middle of May, 1936. A cast was applied, but several days later a Steinman pin was inserted in order to secure better alignment of the fragments. General examination was negative, and urinalysis and Kahn test of the blood were essentially negative. The spinal fluid had been examined because of an acute psychosis, which was undoubtedly due to alcoholism; it was found to be normal. *Staph. albus* infection occurred in the wound of the leg. A hemogram revealed moderate anemia. For several weeks there was a daily elevation of temperature of 2° to 4° F. On July 10, 1936, he was discharged from the Gallinger Municipal Hospital in a light plaster cast.

While at home, on July 14, 1936, the patient suddenly developed an excruciating pain in the right thigh, "as if the muscles were being torn from the leg." This began at 9 P.M., about 5 minutes after he had had an alcohol rub. After about an hour the pain had traveled down to the leg and foot, where it persisted for 10 days and then slowly disappeared. At the onset the leg and foot were blanched except for a few bluish streaks

along the calf. After 3 or 4 days normal color gradually returned, but moderate swelling of the leg and foot developed.

On admission to the hospital on August 17, 1936, the right leg and foot were found to be still slightly painful and somewhat edematous. The color was almost normal, but the foot was a little cool and the pulsations were not palpable in its vessels. Arteriograms were made, and the patient was discharged in a few days.

The patient remained quite well and the fracture and wound of the left leg slowly healed. On September 3, 1936, he was carefully reexamined. He stated that he had been in excellent health prior to his accident but had gained weight (up to 270 pounds) during the preceding 5 years and had had some dyspnea on exertion. Since April, 1936, he had taken digitalis intermittently. Physical examination did not reveal any arteriolar changes in the retinae. The heart was apparently not enlarged and there were no murmurs. The cardiac rhythm was regular and the rate 100 per minute. The blood pressure was 190 systolic and 90 diastolic. The right foot blanched a little more than the left when it was elevated, but both feet retained fair color. Both feet became cyanotic when they were dependent. The legs and feet were slightly edematous and a little cool. Pulsations were not palpable in the feet.

Description of Arteriogram. An artist's exact pen and ink reproduction of the arteriogram made August 19, 1936, is shown in Fig. 1. The lower end of the femoral artery is missing for several centimeters, but its lumen is essentially normal in diameter above and below this area, which represents a completely occluded segment of the vessel. Just below this segment the wall of the vessel shows a slight indentation, which may indicate an arteriosclerotic plaque. Both above and below the occluded portion medium-sized branches of the artery are shown. Those above are mainly muscular branches, while those just below are anastomotic branches about the knee. One in particular is seen to pass downward in an undulatory course from the femoral artery just at its upper point of occlusion and undoubtedly empties directly into the upper portion of the popliteal artery, constituting a short detour of the current of blood around the obturated portion and thus maintaining the function of the main vessel below.

CASE 2.—Clinical History. W. P., an old white man, aged 70, entered the Gallinger Municipal Hospital on August 20, 1936. Two weeks before a blister had appeared at the base of the right little toe; it was opened, and a few days later began to discharge pus. The foot became red and swollen. There had been no previous illness or symptoms referable to arteriosclerosis of any organ or extremity. Physical examination was essentially negative except for the extremities. The blood pressure was 176 systolic and 80 diastolic. The radial arteries were moderately hard. The left posterior tibial artery pulsated well, but the pulsation of the left dorsalis pedis artery was feeble. Neither the posterior tibial nor the dorsalis pedis could be felt to pulsate on the right. A round ulcer about 2 cm. in diameter was present on the lateral surface of the right foot at the base of the little toe. It was shallow and black and a small amount of pus was exuding. The right side of the foot was red and moderately swollen. The oral temperature was never above 99° F. Laboratory studies gave essentially normal results. Continuous hot magnesium sulphate soaks were instituted, and the patient was discharged as practically well on September 1, 1936. Arteriograms of the right lower extremity were made by the injection of 15 cc. of thorotrast.

Description of Arteriograms. Figure 2 is an exact drawing of the arteriogram of the right thigh. It shows absence of a shadow of the femoral artery above its lower half. The vessel below this point has a very irregular, "saw-tooth" lumen indicative of advanced arterio-

sclerosis. Undoubtedly there was complete occlusion of the femoral artery in most of its upper half, probably from just below the femoral triangle where the contrast medium was injected. A number of medium-sized arteries are seen descending from the upper portion of the thigh, branches no doubt of the femoral artery above the occluded portion. A tortuous one on the medial side of the femur is seen to empty directly into the femoral artery below the occluded portion.

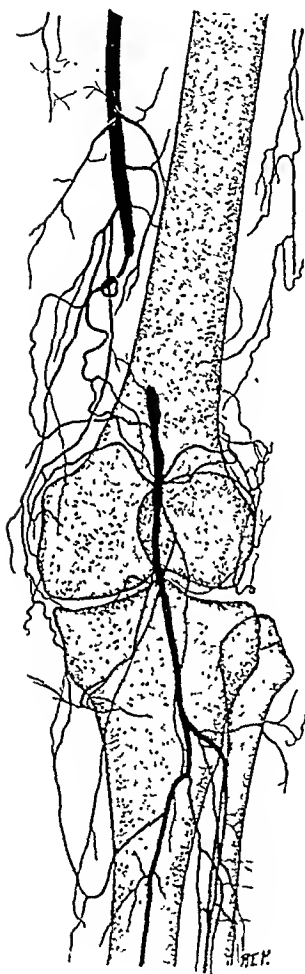


FIG. 1

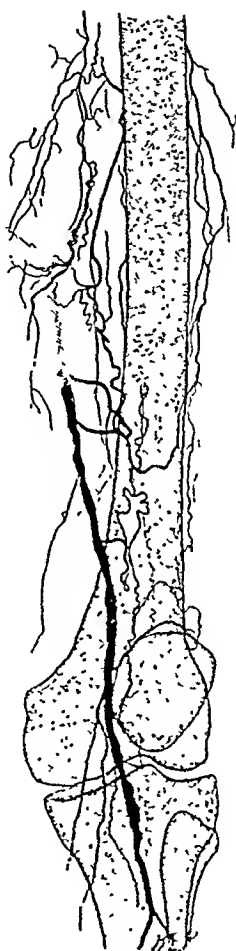


FIG. 2

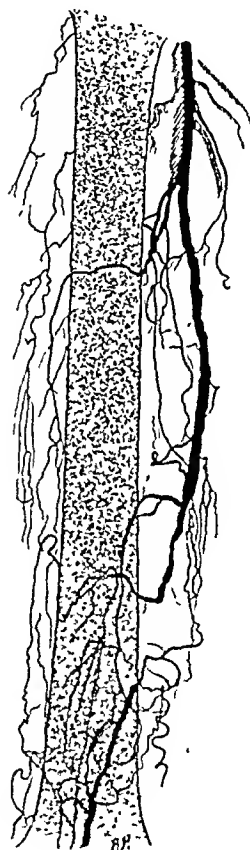


FIG. 3

FIG. 1.—(Case 1.) Exact drawing of arteriogram, showing evidence of complete occlusion in lower portion of femoral artery and collateral arteries connecting the lumen above and below.

FIG. 2.—(Case 2.) Exact drawing of arteriogram of thigh, showing evidence of occlusion of upper half of femoral artery and collateral arteries emptying into the arteriosclerotic femoral artery below.

FIG. 3.—(Case 3.) Exact drawing of arteriogram of thigh, showing markedly arteriosclerotic femoral artery with an area of occlusion in its lower third. Collateral arteries anastomose between the portions of the artery above and below this area.

The arteriogram of the leg showed absence of the shadow of the anterior tibial artery, which was probably completely occluded by atherosclerosis. However, many fine collateral arteries were demonstrated which probably assumed its function. The posterior tibial artery was seen to be occluded in its lower half but appeared again with a very narrowed lumen behind the internal malleolus. However, the occluded portion was bridged across by fine, long collateral vessels, which above were very undulatory.

CASE 3.—Clinical History. F. C., a white man, aged 68, entered the Gallinger Municipal Hospital on January 14, 1937, complaining of loss of strength, some weakness of the left leg, moderate dyspnea on exertion, constipation and dysuria. He was found to have pernicious anemia, moderate essential hypertension, urethral strictures and prostatic hypertrophy. During the course of the physical examination the pulsations of the left popliteal artery were found to be feeble, and pulsations were not felt in the left posterior tibial and dorsalis pedis arteries. The right dorsalis pedis artery pulsated feebly, and the right posterior tibial artery did not pulsate. However, there were no color changes or trophic disturbances of either foot. The history did not reveal any suggestion of previous vascular trouble in the extremities. An arteriogram of the left thigh was made by means of 10 cc. of thorotrast, of which Fig. 3 is an exact line drawing.

Description of Arteriogram. The femoral artery has a very jagged border, due undoubtedly to arteriosclerotic changes. In the lower third of the arterial shadow there is a short gap, the result certainly of complete occlusion of the lumen. However, collateral arteries are numerous throughout the thigh; and a number of these arteries anastomose between the upper and lower segments of the femoral artery, allowing blood flow to continue through the main artery below the occluded portion.

Discussion. Arteriography is teaching us many things about the mechanics of the circulation in vascular disease which are not demonstrable otherwise. In Case 1 we see how Nature restored the function of a main artery by sidetracking the blood from above an occluded portion of the artery through a branch and bringing it back to the main trunk below. Undoubtedly other collateral arteries aided in this restoration. The history suggests embolism, but more probably sudden thrombosis occurred. The restorative alterations were made within a month of the time of occlusion.

Case 2 is quite different from Case 1. Here the occlusive process apparently developed very slowly, being due to gradual diminution of the lumen by atherosclerosis. But again we see the same detour of the blood through smaller arteries back to the main artery. Case 3 was similar to Case 2 in that the occlusive process was undoubtedly a very slow one due to atherosclerosis.

Readjustment of the circulation of the lower extremity by direct anastomosis allows one to make a better prognosis than in cases in which the main arteries are completely obliterated and in which the circulation is entirely dependent upon smaller vessels. In Cases 1 and 3 there was no gangrenous process, and in Case 2 trophic changes were minor and healed readily.

In cases of embolism in which recovery ensues it may be that the circulation in an extremity is reestablished in the manner described,

at least at times. Arteriotomy as advocated by Leriche may be efficacious in that such a procedure conceivably may stimulate the development of direct anastomoses as well as the collateral circulation in general.

Only one illustration of a case similar to these could be found in the literature. This was Case 20 (p. 377) of Demel, Sgalitzer and Kollert.³ It is probable, however, that such cases have been observed in large clinics where arteriography is frequently employed.

It is believed that most collateral vessels are merely enlarged and elongated branches that existed prior to the onset of vascular disease. Such cases as those described indicate that at times new anastomoses may develop, however, since it is quite improbable that a branch of an artery normally empties into the same artery a short distance below its origin.

REFERENCES.

- (1.) Allen, E. V.: *Arch. Int. Med.*, 57, 601, 1936. (2.) Allen, E. V., and Camp, J. D.: *J. Am. Med. Assn.*, 104, 618, 1935. (3.) Demel, R., Sgalitzer, M., and Kollert, V.: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 42, 357, 1930-31. (4.) Veal, J. R., and McFetridge, E. M.: *J. Am. Med. Assn.*, 104, 542, 1935. (5.) Yater, W. M.: *Am. Heart J.*, 12, 383, 1936; *Ann. Int. Med.*, 10, 466, 1936.

THE RESPIRATORY BASIS OF PERIODIC SUBCOSTAL PAIN IN CHILDREN.

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A "stitch in the side," first described by Pliny the Elder, is a frequent complaint of school children. As a harmless symptom it is often confused with gastro-intestinal, nervous or cardiac disturbances and occasionally as a rheumatic manifestation. The child in the midst of some effort gets a pain in the side, becomes pale and must rest for relief. If the pain does not pass immediately deep breathing, particularly exhalation, will alleviate the tense feeling. In every case the pain comes upon the child in motion, especially during quick jerks or jars of the body in the course of walking, running or some other activity involving effort. The site of the pain is usually below the costal margin, and contrary to other types of abdominal pain in children, subcostal pain is described and localized by them as a clear-cut experience.

Subcostal pain has been regarded as a transient circulatory disturbance in abdominal viscera by Mosler,⁷ as a perisplenic phenomenon by Schmidt,¹³ as a stigma of constitutional weakness by Benjamin,³ as an index of sudden changes in the volume of the spleen by Bancroft,² as contraction of the spleen by Rautmann and Morse,¹² as a spasm of the intercostal muscles by Pembrey,¹⁰ as

splenic tension by Mosse,⁸ as irregular respiration by Herxheimer,⁶ as reversed breathing by Nassau.⁹ We sought the basis of this phenomenon in terms of the common findings characterizing the children complaining of periodic subcostal pain.

Required health examinations of 500 school children revealed 56 complaining of periodic subcostal pain on exertion. The complaint was usually volunteered by the child or parent rather than elicited by the physician. In each case, the nature, site and frequency of the subcostal pain were clearly represented during the examination. While other children were found on careful questioning to have similar experiences they were less well-defined and hence excluded from this study. The children with the periodic subcostal pain were therefore studied to determine the factor or factors common to this group.

RESULTS. 1. *Age and Sex of Group.* The children studied consisted of 24 boys and 32 girls, between the ages of 7 and 16 years. Whether the girls were more apprehensive about their person and hence more outspoken than the boys was difficult to determine, for sex did not appear to be a factor in the causation of subcostal pain. The distribution of age was as follows:

Age (years):	7	8	9	10	11	12	13	14	15
Boys	1	1	1	2	3	3	5	5	3
Girls	0	2	1	4	4	5	5	6	5

Increase in the frequency of subcostal pain with the onset of puberty exists despite the fact that the total number of children examined between 6 and 10 years of age exceeded those between 10 and 15. While the condition becomes manifest at 7, it is relatively infrequent until the beginning of the tenth year. The significance of age as a causative factor will become apparent from subsequent considerations.

2. *Site and Frequency of Pain.* Localization of the pain was clearly defined by all children studied. This was considered significant because in all other types of pain children usually point to the umbilical region as the area of involvement. This type of pain however was described clearly by each child, as a single site for most children and multiple in the remainder. Indeed the site, side and occasion of the pain were confirmed by repeated citations at subsequent examinations. Attempts to precipitate the pain in conformance with the description was difficult. Nevertheless, it was possible in several instances to initiate the experience by having the child twist his body with a quick jerk towards the side usually affected.

Twenty-six children experienced pain on the left side, 20 on the right and 10 on both sides. The distribution of the site of the pain was as follows: the spleen, 27 cases, liver 14, stomach 6, diaphragm 5

and heart 4. Most of the children experienced the pain on exertion, some daily but the majority about once or twice a week. Of the 56 children 3 occasionally felt the pain while resting in any position. In fact 1 of them sensed the pain by suggestion and had to double over to overcome it. All sorts of activities were considered responsible factors; 41 children complained of experiencing the pain during fast walking, 24 on running, 32 from athletic activities, 12 from dancing, 8 after meals.

3. *Body Build and Posture.* The linear type of body build was more common than the others complaining of subcostal pain. The distribution of body build was 21 cases of linear, 15 lateral, 15 medial and 5 muscular. The linear type children were hypertonic and all other types were hypersensitive emotionally. The striking feature common to all was poor postural alignment particularly of the kypholordotic type. In severe cases the flat chested child with a curved upper back, forward neck and shoulders showed some obstruction to breathing. The lower back compensates with a moderate to marked lordosis and a somewhat prominent abdomen.

4. *Breathing Patterns.* Every child susceptible to subcostal pain on exertion reported the prompt cessation of the pain with forced deep breathing particularly exhalation. With this as the acknowledged procedure for recovery we studied the relation of breathing to this phenomenon as the etiologic factor. The breathing space in the upper respiratory tract was inadequate in 26 of the children studied, the rest being normal. The distribution of children with obstructed breathing was as follows: chronic sinusitis, 12 cases, allergic rhinitis 10, enlarged adenoids 4.

The type of breathing of each child studied was determined from the recumbent resting position. The child was observed sideways for the silhouette view of the profile of the whole trunk in order to compare the degree of forward movement of the thorax and abdomen. Then the child was observed face to face to determine the relative parts played by the diaphragm and trunk muscles in both quiet and exaggerated breathing. Four types of breathing were noted in these children. First, thoracic, second abdominal, third simple thoracic-abdominal and fourth crossed thoracic abdominal. *Crossed thoracic-abdominal* type of breathing, first described by Czerny,⁴ involves an oblique movement for each phase of breathing. The upward expansile inspiratory movement of the chest is so extensive that the increase in the size of the cavity is altogether too great for the lungs to fill. As a consequence the abdominal viscera, liver, stomach, and so on, are actually drawn upward into the chest by negative pressure instead of getting pushed downward and forward as in other types of breathing. The diaphragm is thus followed up into the chest cavity with a consequent depression instead of a protrusion at the pit of the stomach. The reverse of course main-

tains on expiration. Accordingly, the sinking of the thorax during expiration is accompanied by a forward thrust of the abdominal wall.

The distribution of the type of breathing was as follows: 29 showed crossed thoracic-abdominal type, 7 thoracic type and 5 simple thoracic-abdominal type. Although each type of breathing appeared natural for each type child, the respiration was far from effective during exertion. This was particularly evident with the 29 children who showed crossed type of thoracic-abdominal breathing. There was apparent limitation in the range of respiratory function; some could not execute a movement which would completely fill the lungs; some could not voluntarily use the costal and abdominal muscles separately; some could not relax the abdominal muscles during inspiration; some found it difficult to draw up the chest and expand the abdomen at the same time. With the group as a whole it became apparent that on the slightest additional demand the respiration became relatively insufficient.

We therefore determined the vital capacity of the lungs. Each child was requested to blow the largest possible breath into a wet-type spirometer. Several trials were allowed and the best figure that could be approximately repeated was taken as the proper value. The temperature of the water was maintained constant to prevent erroneous variations in volume. The number of readings for each child was too few to necessitate correction for practised performance. Since the conditions of each determination were individual, no one type of standardized procedure was followed. The measurement of vital capacity is a problem of understanding and coöperation by the child as well as one of lung capacity and chest flexibility.

The vital capacity values obtained were compared with the Baldwin standards of breathing capacity-height-age for both boys and girls,¹ and found to be consistently below the average norms. The number of children measured at each age group was too few to calculate the standard deviation or the coefficient of variation. The consistently low breathing capacity is significant because most of the children with subcostal pain were of the linear build which normally have a relatively higher vital capacity for height than do the lateral type of children. The children studied were obviously free from any pathologic conditions of either heart or lungs. The low normal levels of vital capacity in this group of children apparently related to their limited respiratory mechanisms.

5. *Therapy.* The respiratory deviations common to all children with subcostal pain were improved by specific therapeutic measures—clearance of obstructed breathing, correction of breathing patterns and postural defects. Paralleling the medical care of the upper respiratory tract some children were required to perform daily postural¹¹ and breathing exercises.⁵ These were checked indi-

vidually in posture classes under the direction of a physiotherapist. Physical examinations were made at 2- or 3-week intervals and vital capacities were redetermined after the third month. Within this period the subcostal pain ceased to reappear even with strenuous effort. But there was a marked individual variation in the therapeutic response of each child. In 40 cases the vital capacity was

TABLE 1.—BREATHING CAPACITY DETERMINATIONS.

Boys.					Girls.				
Age, yrs.	Case.	Height, inches.	Vital capacity, cc.		Age, yrs.	Case.	Height, inches.	Vital capacity, cc.	
			Before.	After.				Before.	After.
8 . .	M. B.	48.4	1340	1375	8 . .	C. A.	45.5	1050	1150
9 . .	K. G.	52.3	1610	1690		D. D.	48.8	1275	1300
10 . .	W. C.	59.0	2175	2280	9 . .	D. A.	53.7	1610	1690
	G. S.	55.5	1910	2020	10 . .	F. B.	54.0	1640	1700
11 . .	A. K.	60.8	2310	2500		J. G.	55.5	1785	1810
	J. J.	61.5	2495	2625		R. B.	57.0	1840	1920
	I. R.	56.5	2030	2175		S. T.	56.8	1910	1890
12 . .	C. L.	62.0	2500	2610	11 . .	B. S.	55.4	1740	1820
	E. M.	58.4	2180	2250		A. S.	56.0	1810	1860
	H. N.	60.1	2375	2450		E. T.	57.3	1850	1950
13 . .	S. B.	61.5	2600	2725		N. S.	58.5	2055	2125
	R. O.	62.0	2650	2710	12 . .	W. K.	58.0	2010	2075
	F. S.	63.8	2810	2925		P. Z.	59.5	2125	2250
	B. N.	64.5	2930	3050		D. F.	61.0	2280	2380
	T. V.	66.0	3050	3340		J. A.	61.2	2310	2390
14 . .	K. H.	61.2	2680	2790		L. I.	62.8	2490	2610
	F. T.	63.5	2960	3070	13 . .	E. J.	57.9	2010	2100
	A. G.	65.5	3200	3440		N. O.	59.1	2120	2250
	P. O.	68.0	3560	3550		I. H.	60.2	2250	2310
	R. C.	69.3	3550	3740		F. H.	61.8	2475	2525
15 . .	A. S.	64.5	3260	3250		A. L.	63.1	2500	2610
	T. K.	69.5	3950	4160	14 . .	M. J.	61.5	2480	2625
	J. R.	70.0	4060	4010		F. S.	63.2	2600	2690
						S. G.	63.9	2675	2755
						R. C.	64.6	2780	2900
						H. H.	65.7	2890	2925
						C. N.	66.1	2900	3010
					15 . .	M. M.	61.9	2580	2610
						S. L.	63.6	2800	2850
						L. F.	64.6	2790	2910
						S. G.	66.1	2925	3050
						F. H.	66.2	2900	3090

markedly increased on assuming the corrected posture and improved breathing pattern; 14 cases were moderately altered; 8 developed a lowered breathing capacity which persisted in 2 cases. Improved vital capacity meant an increased latitude for diaphragmatic and thoracic excursion. Respiration was apparently facilitated and became deeper and somewhat slower.

Postural improvement was attained in terms of individualized criteria. With the marked individual variations in body build no one standard could be set up to define mechanically the best alignment for each child. Good posture was adjudged by the increase in the anteroposterior spinal curve, by the elevation of the chest in the position of almost full inspiration and by a firmness of the upper portion of the abdomen anteriorly. The habitual maintenance of such posture required many months because conditioned reflexes are acquired very slowly. Assiduous attempts at correcting faulty posture in 8 of the children studied put so great a task on the musculature of the thorax and abdomen that the vital capacity actually diminished. Indeed the subcostal pain previously experienced at infrequent intervals now became more frequent, particularly after the strenuous postural and breathing exercises. But with adjustment of the correction tasks to the children individually the stance improved and the subcostal pain cleared as with all the other children studied except in 2 cases.

Conclusions. 1. Required health examinations of 500 school children revealed 56 (24 boys and 32 girls) between the ages of 7 and 16 years, complaining of periodic subcostal pain on exertion.

2. Twenty-six children experienced pain on the left side, 20 on the right and 10 on both sides, the pain being referred to the spleen, liver, stomach, diaphragm and heart respectively. The pain occurred on exertion about once or twice a week during fast walking, running and participating in athletic activities or after meals.

3. Periodic subcostal pain occurred most frequently in the linear and medial types of body build with a kypholordotic postural defect. The pain was predominant in children with crossed thoracic-abdominal breathing and the abdominal type of breathing respectively, respiration proving ineffective on exertion.

4. Vital capacity determinations, obtained with a wet type spirometer and compared with the Baldwin standards of breathing capacity for height and age in boys and girls, were consistently below average norms.

5. Periodic subcostal pain ceased to recur in 48 out of 56 children after 3 months of daily postural and breathing exercises.

REFERENCES.

- (1.) Baldwin, B. T.: *Am. J. Phys. Anthr.*, 12, 247, 1928. (2.) Bancroft, J.: *Ergebn. d. Physiol.*, 25, 818, 1926. (3.) Benjamin, K.: *Jahrb. f. Kinderh.*, 102, 203, 1923. (4.) Czerny, A.: *Monatsch. f. Kinderh.*, 14, 1, 1916. (5.) Flack, M.: *Lancet*, 2, 741, 1921. (6.) Herzheimer, H.: *Deutsch. med. Wchnschr.*, 57, 1130, 1927. (7.) Mosler, F.: *Ziemssens' Handbuch*, 2d ed., Leipzig, F. C. W. Vogel, vol. 8, 1878. (8.) Mosse, M.: *Med. Welt.*, 1, 17, 1927. (9.) Nassau, E.: *Klin. Wchnschr.*, 14, 1252, 1935. (10.) Pembrey: *Loc. cit.*, p. 5. (11.) Phelps, W. M., and Kiputh, R. J. H.: *Postural Defects*, Springfield, Ill., Charles C Thomas, 1932. (12.) Rautmann, H. L.: *Med. Welt.*, 1, 1047, 1927. (13.) Schmidt, F. A.: *Unser Körper*, Voigtlander, Leipzig, 1929.

THE ANEMIA OF MYXEDEMA: ITS CLASSIFICATION AND TREATMENT.

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It has long been known that a moderate degree of anemia is the usual accompaniment of myxedema.^{4,9-11,18,28} However, in the clinical literature, one finds considerable disagreement, not only as to the type of anemia that is characteristic of myxedema, but also, as to its proper treatment. During the past 4 years, 20 cases of moderate to severe hypothyroidism have been studied in our hospital and out-patient departments. In each instance the metabolic rate was below -20% . The hypothyroidism was associated with an anemia in 9 instances (44%), of which 8 had adequate diagnostic and follow-up blood studies. In 2 of the patients, a diagnosis of both pernicious anemia and myxedema were made, and in a third case, the presence of pernicious anemia was questionable. These 3 cases will not be considered in this report. The remaining 5 served as a basis for attempting to correlate the clinical observations in the anemia of myxedema with our previous experimental findings.^{23a,b}

Case Reports. CASE 1.—Mrs. A. M., a 42-year-old white female, entered our Outpatient Department, May 1, 1936. Her mother had died of pernicious anemia at the age of 58. In addition to the patient's typical symptoms and signs of myxedema that had been present for about 12 years, there was a well marked lemon-yellow pallor of the skin, a moderate papillary atrophy of the tongue, and bilateral sluggish deep and superficial reflexes. The vibratory sense was intact.

The blood count disclosed a hemoglobin of 69% (11.7 gm.), erythrocytes 3,860,000, and leukocytes 5700 with a normal differential count. The mean corpuscular volume was 87 cu. microns, the mean corpuscular hemoglobin 30.5 micromicrograms. The icterus index was normal; the reticulocytes 0.1%. A normal amount of free hydrochloric acid was present in the gastric content, and the stool was negative for blood. The basal metabolic rate was -43% .

Before thyroid extract was started, the patient was given 3 cc. of liver extract (Lederle), intramuscularly, on 3 successive days. During the following 10-day period, there was no increase of the reticulocytes. Thyroid extract, 4 grains daily, was then given followed by a prompt rise in the metabolism, but with no effect on the number of reticulocytes. Six weeks after taking thyroid extract, the hemoglobin was 64% (10.8 gm.), the erythrocytes slightly decreased to 3,300,000. The addition of iron and ammonium citrate, 90 grains a day, to the maintenance dose of thyroid extract, produced a slow but sustained increase in the hemoglobin to 87% (14.7 gm.), and in the erythrocytes to 5,330,000 (Fig. 1).

With improvement in the blood, the tongue and neurologic changes completely disappeared.

CASE 2.—Mrs. L. C., a 30-year-old white female, entered this hospital, May 20, 1935, with a history of diabetes for 7 years. A year before admis-

sion, she had first noted a progressive weakness, lemon-yellow pallor, dyspnea and palpitation on exertion, and numbness and tingling of the extremities. The physical examination disclosed a rather obese, slightly icteric, pale individual with a dry scaly skin. The tongue was pale and smooth. All deep and superficial reflexes were sluggishly present, and the vibratory sense was absent below the knees.

The blood count showed a hemoglobin of 65% (11 gm.), erythrocytes 3,090,000, and leukocytes 4200 with a normal differential formula. The mean corpuscular volume was 93 cu. microns, and the mean corpuscular hemoglobin 32% micromicrograms. The icterus index was 25 units, the reticulocytes were 0.55%. The bleeding and clotting time were normal, as well as the fragility of the red blood cells. There was a persistent achlorhydria of the gastric content, even after histamine stimulation. There was very slight occult blood present in the stool. The hyperglycemia and glycosuria, a difficult problem, does not concern us in this report.

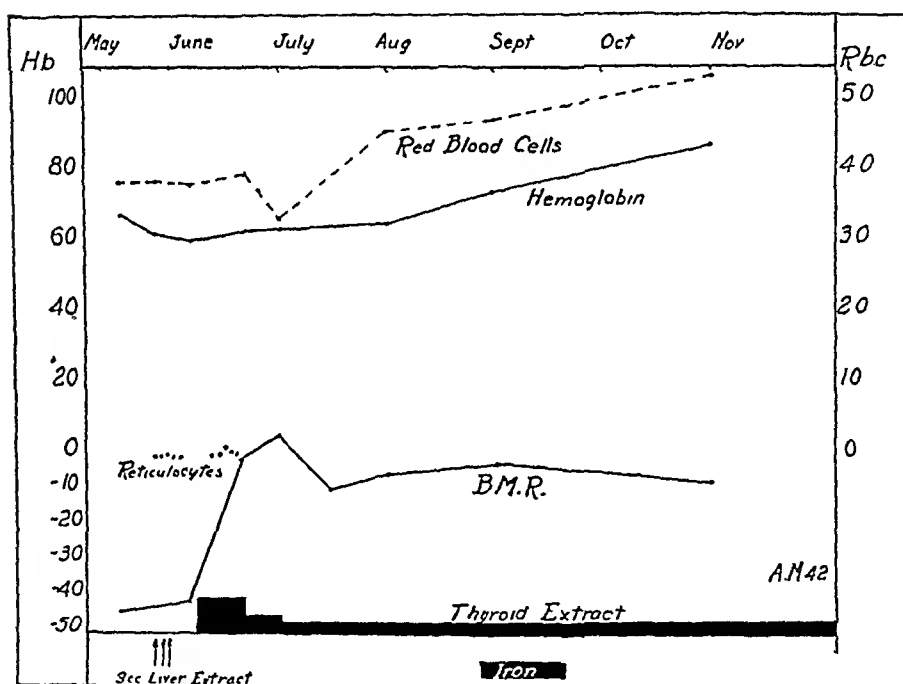


FIG. 1

A diagnosis of pernicious anemia was made, although her age and the absence of distinct macrocytosis was against it. Further doubt as to this diagnosis was expressed when, after receiving daily doses of intramuscular liver extract for 3 weeks, no effect on the reticulocytes had been noted. The daily administration of 90 grains of iron and ammonium citrate, first alone, and later in combination with oral and parenteral liver extract, failed to cause any significant change in the blood (Fig. 2A). It was not until Dr. Frank Conlin first saw the patient, 16 weeks after admission, that myxedema was recognized and a basal metabolic rate obtained and found to be -43%.

Though thyroid extract caused a prompt improvement in the patient's general condition, a temporary decrease of the blood counts was again noted during the first 2 months of treatment. During 7 months of thyroid therapy, without liver or iron, both the hemoglobin and the number of erythrocytes

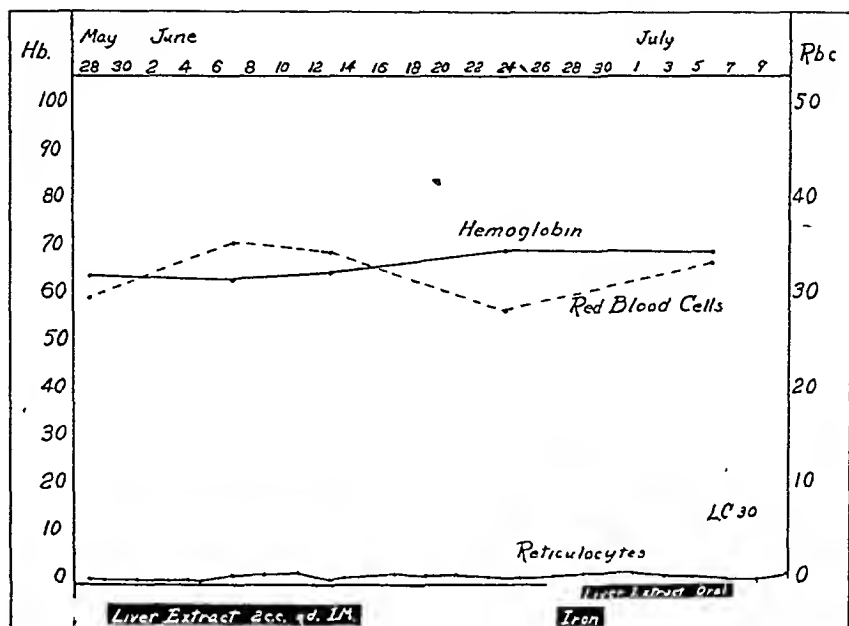


FIG. 2 A

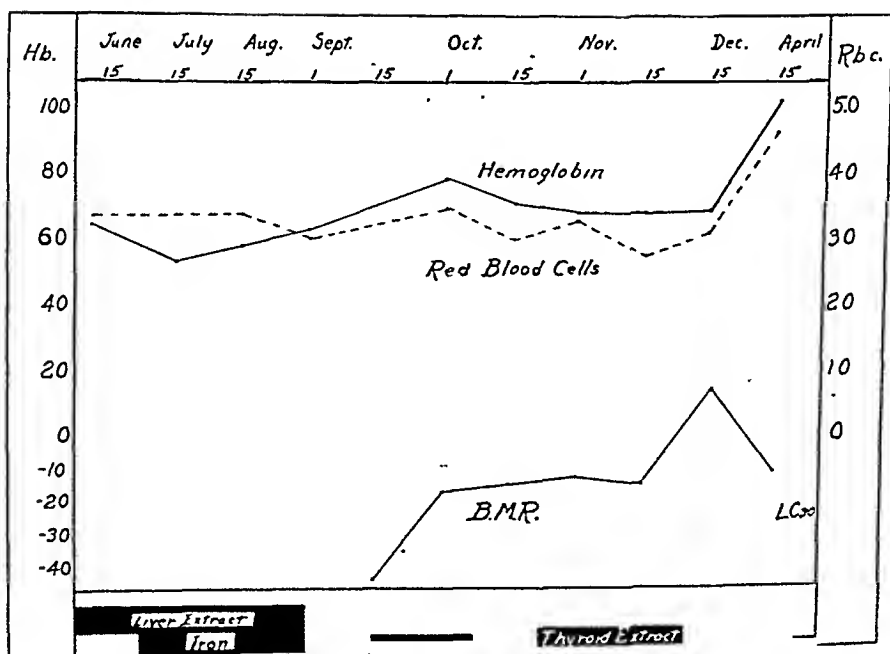


FIG. 2 B

slowly increased and finally reached and remained within normal limits (Fig. 2 B). During this time, there was no significant change in either the mean corpuscular volume or hemoglobin content of the red blood cells. There was a progressive decrease of the icterus index. The achlorhydria persisted. The tongue regained its normal appearance and the paresthesias disappeared with return of the blood counts to normal.

CASE 3.—Mr. G. O., a 28-year-old white male patient of Drs. F. W. Niehaus and W. D. Wright, complained of weakness, fatigue, and chilly sensations for 1 year. When examined, September 4, 1935, no abnormality could be found except for a slight pallor. There were no tongue or neurologic changes.

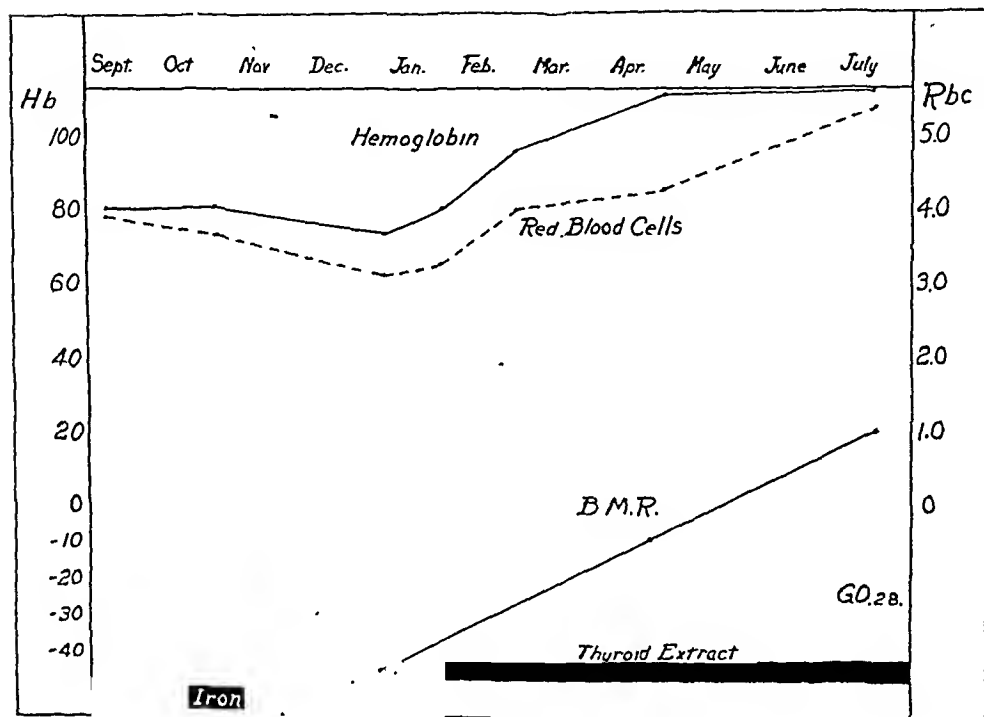


FIG. 3

The hemoglobin was 82% (14.2 gm.), the red blood cells 4,100,000, with a normal total and differential white blood cells count. For the next 4 months, the symptoms persisted in spite of 45 grains of iron and ammonium citrate daily. The anemia progressed to 76% (13.2 gm.) hemoglobin, and 3,250,000 erythrocytes. Further study of the blood then revealed the mean corpuscular volume to be 92 cu. microns, and the mean corpuscular hemoglobin 41 micromicrograms. The icteric index was normal. There was free hydrochloric acid present in the gastric analysis.

At this time, the possibility of hypothyroidism was recognized; the basal metabolic rate was -37%. Iron medication was then discontinued and thyroid extract, 2 grains daily, substituted. The improvement in the blood was roughly parallel to the increase in the metabolic rate and the patient's general well being. After 6 months of thyroid extract, the hemoglobin was 106% (20.2 gm.), and the erythrocytes 5,470,000 (Fig. 3).

CASE 4.—Mrs. S. P., a 53-year-old white female patient of Dr. E. J. Kirk, was first seen January 7, 1935, presenting typical symptoms and signs

of myxedema of about 6 years' duration. In addition, there was a moderate hypertension.

Before thyroid medication, the blood counts were normal with a hemoglobin of 88% (18.9 gm.), erythrocytes 4,500,000 and leukocytes 6400 with a normal differential formula. Hematocrit determinations were not made on this patient. Free acid was present in normal amounts in the gastric analysis. The basal metabolic rate was -25%.

Three weeks after a daily dose of 4 grains of thyroid extract, the metabolic rate had increased to +20%, but the hemoglobin had dropped to 69% (11.7 gm.), and the red blood cells to 3,700,000. Two months later, the blood returned to its previous normal level (Fig. 4).

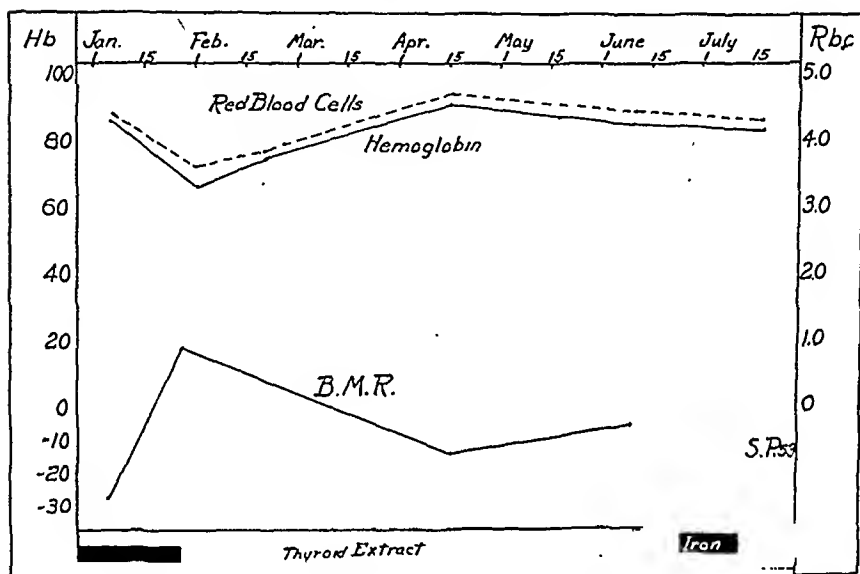


FIG. 4

CASE 5.—Mrs. M. C., a 50-year-old white female, entered the Out-patient Department, January 3, 1934, presenting the characteristic symptoms and signs of a severe hypothyroid state. After a subtotal thyroidectomy for a toxic adenoma, 4 years previous to entrance, she had gained 70 pounds in weight.

A blood count was not done on her first examination. The basal metabolic rate was -31%. She was advised to take a daily dose of 6 grains of thyroid extract. When the metabolism reached normal levels, 1 month later, this dose was decreased to 3 grains a day. Though most of her symptoms of myxedema quickly disappeared, the pallor, glossitis, and paresthesias of the hands and feet persisted.

Examination of the blood at this time revealed the hemoglobin to be 68% (11.5 gm.), the red cells 3,550,000, and the leukocytes as 6200 with a normal differential. Hematocrit determinations were not done, but from the blood smear, the erythrocytes appeared to be microcytic in character. There was no free acid found in the gastric content. Iron, in the form of Bland's, 10 grains 3 times a day, was added to the thyroid extract; but after 5 months, there had been very little effect on the blood. The hemoglobin was 71% (12 gm.), the red blood cells 3,880,000 and the leukocytes 7600. The

mean corpuscular volume was 72 cu. microns, the mean corpuscular hemoglobin was 26 micromicrograms. The basal metabolic rate at this time was -12% . In order to facilitate better absorption of iron in the gastrointestinal tract, hydrochloric acid was given in conjunction with iron and ammonium citrate, 90 grains a day. This procedure seemed to result in a prompt improvement in the blood count to normal values and greatly improved the glossitis and paresthesias. However, because of a misunderstanding of orders, the patient did not receive any thyroid extract for 1 month, and then for several more months, inadequate doses, all of which resulted in a progressive decrease of the basal metabolic rate to -24% and the return of many unpleasant symptoms.

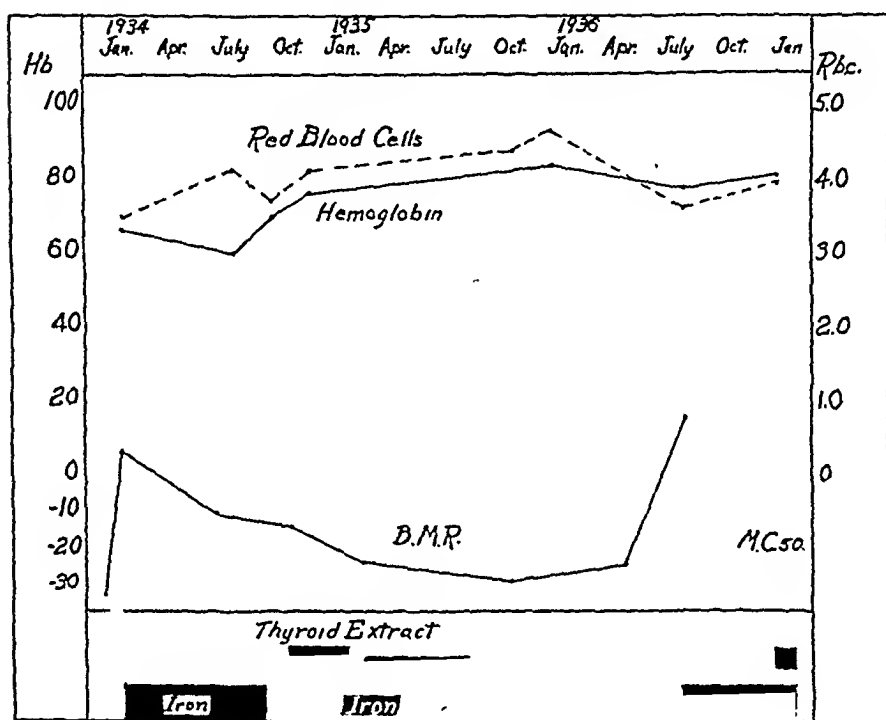


FIG. 5

The blood counts remained within normal limits in spite of this long period of hypometabolism. Again, however, with an increase of thyroid medication and the raising of the metabolism, the blood counts showed a transient decrease (Fig. 5).

Discussion. Though it was not a prominent feature, Stone²⁴ found anemia present in 56% of his 23 myxedematous patients, and in Lerman and Means^{14a} series, anemia was noted in 60% of the cases. The incidence of anemia in myxedema was not quite as high in our series of cases (44%). In our first 4 cases, the myxedema was classed as "spontaneous" in origin; in the remaining case, the hypothyroidism followed subtotal removal of the thyroid gland. All our cases were adults, 4 females and 1 male.

Etiology. The etiology of the anemia of myxedema is still an unsettled question. It is not known why anemia develops in approx-

imately one-half the cases of myxedema, whereas in the other half, equally as severe, the blood remains normal. Our observations are in accord with Emery's⁵ who found no relation between the degree of anemia and the metabolic rate, or the duration of the disease. Lerman and Means^{14b} add that 53% of their patients with myxedema showed an achlorhydria, and that the anemia is more likely to develop in those patients. Of our 20 patients, 11 had an analysis of their gastric juice, with 5 showing achlorhydria (45%). Though all 5 cases were associated with an anemia, in the other patients presenting as severe an anemia, the gastric acidity was normal. In our opinion, achlorhydria may very well serve as a conditioned deficiency in accentuating the production of anemia, but it is apparently not absolutely essential in the etiology.

MacKenzie,¹⁷ Stone²⁴ and Minot²⁰ believe that the anemia results from a deficient manufacture of blood cells in the bone marrow due to the sluggish oxidation that occurs in all tissues during the hypometabolic state. This explanation seems substantiated, experimentally, by Esser,⁶ Orr,²¹ Kunde, *et al.*,¹² and ourselves,^{23a, b} all working with totally thyroidectomized rabbits, and uniformly producing an anemia that responded to thyroid extract.

The question naturally arises as to whether a plasma volume shift with a resulting hydremia could possibly account for the blood changes in myxedema. That this is not the case, and that the anemia in myxedema is real and not apparent is based on the work of Friedländer *et al.*,⁷ who found a sharp decrease in blood volume following thyroidectomy in male cats. Moreover, Thompson²⁶ concluded from his clinical observations that, 1, in myxedema, as the weight increases, the total plasma volume decreases; and 2, in myxedema, there was frequently a decrease of total blood volume of 25%. This total plasma and blood volume decrease in myxedema should then cause a concentration of the cellular content of the blood, and not, as in some cases of myxedema, a low hemoglobin and erythrocyte count. Though this possibility of a blood volume shift is now under our investigation, it is probably not the explanation of the anemia of myxedema. However, a plasma volume increase in myxedema following the administration of thyroid extract may explain the transient decrease of hemoglobin and erythrocytes that we so often noted during the first few weeks of therapy. This decrease is well exemplified in Case 4, and to a much lesser degree in Cases 1, 2, and 5.

Symptoms and Signs. In addition to the usual characteristic features of myxedema, the anemic patient may present such clinical manifestations as a light lemon-yellow pallor, glossitis, and paresthesias. The icteric tint of the skin is not due to increased bile pigment in the blood stream, as is the case in pernicious anemia or familial hemolytic anemia.²⁰ In our group, the icterus index was normal in 3 cases, moderately elevated in 1 case and not determined

in the remaining patient. We have observed the fiery-red, sore tongue in 1 patient (Case 5), and the bald, smooth, pale tongue in 2 others (Cases 1, 2). Pitfield²² and Means, Lerman and Castle¹⁹ have commented on the neurologic manifestations of myxedema. In our series, numbness and tingling of the hands and feet were present in 3 patients (Cases 1, 2, 5). In each instance, the reflexes were present, but diminished; the vibratory sense was absent in 1 and present in the 2 others. Four months of intensive parenteral liver extract failed to cause any change in these neurologic signs in Case 2, although thyroid extract caused marked improvement in this and in the other 2 cases.

Blood Picture. The reported blood picture in this type of anemia has not been uniformly constant or characteristic. Usually, the degree of anemia is not very marked. The hemoglobin is usually between 50 and 70%; the number of erythrocytes between 3 and 4 million. The reticulocytes are not increased. Some writers have compared the erythrocytes to those found in chlorosis,^{2,27} while others,^{3,17,22,24} have been impressed with the resemblance of this anemia to that of pernicious anemia. Lerman and Means¹⁴ are of the opinion that the anemia may be classed in either group, and that in those patients having achlorhydria, a pernicious instead of the secondary type of anemia may develop.

Experimentally, Kunde *et al.*,¹² working with cretin rabbits, and in our work with the adult animals,^{23a} the anemia was characterized in each instance by a definite macrocytosis and hyperchromia. We have not, however, observed this erythrocytic change clinically; as in the 4 cases in which hematocrit observations were made, 3 showed the mean corpuscular volume and the mean corpuscular hemoglobin to be within the limits of normal variation, *i. e.*, normocytic and normochromic. In the other instance (Case 5), a post-operative case, there was a definite hypochromia present. In this case, the existing achlorhydria may have been a factor in producing, accentuating, or changing the character of the red blood cells through an iron-deficiency. It is obvious that additional hematocrit observations on a large series of myxedematous patients with anemia are necessary before the erythrocyte is definitely classified as normocytic in character.

The discrepancy between the experimental and clinical observations of red blood cell size and hemoglobin content in myxedema may be due to several important factors. In the first place, the amount of functioning thyroid tissue must be considered. Experimentally, we are dealing with animals that have been subjected to a *total* thyroidectomy, following which *each* animal developed an anemia. On the other hand, the majority of the clinical cases of myxedema have been *spontaneous* in origin, and approximately only *half* of these patients develop anemia. Furthermore, in the clinical cases, the presence or absence of the complex diet factors,

gastric achylia, pregnancies, and chronic infectious and toxic processes, and their effect on the hematopoietic system must all be kept in mind. Experimentally, these factors do not complicate the blood picture as we deal with young, healthy animals, of approximately the same age and weight, on a standard diet and under ideal environmental surroundings.

Usually, there is little or no definite change in the leukocyte count or the differential formula, although a slight leukopenia with a slight lymphocytosis may be present. Minot²⁰ concluded that a decreased bone-marrow function was evident, because the anemia was characterized by a moderate leukopenia, a slight lymphocytosis, and often a decrease of the platelet count, without evidence of increased reticuloeytic formation. One would certainly not ascribe the anemia to increased blood destruction in the absence of increased bilirubinemia. To explain the anemia, it may help to study bone marrow biopsies in the clinical cases, and though we have completed such a study in our thyroidectomized rabbits, both before, during and after thyroid feedings, we have not yet arrived at any definite conclusions.

Differential Diagnosis. In the presence of an "anemia," achlorhydria, tongue changes and paresthesias, an erroneous diagnosis of pernicious anemia may be made instead of the anemia of myxedema. Such was our experience in Case 2. Sturgis²⁵ and Minot²⁰ believe that though there is a close clinical similarity between the two, the actual erythrocytic changes in myxedema are different in that the large macrocytes are absent. In our experience, the use of the hematocrit to determine the average corpuscular volume and hemoglobin content of the red blood cells is of utmost value in the differential diagnosis. Furthermore, the presence of a normal gastric acidity and the physical signs of myxedema aid in ruling out pernicious anemia. Of course, the diagnosis of both pernicious anemia and myxedema in the same individual has been made.^{18,19} As mentioned, we have 3 such cases under observation. However, the association must be rare as Giffin and Bowler⁸ found only 2 cases of myxedema in the analysis of 628 cases of pernicious anemia. The basal metabolic rate in pernicious anemia is ordinarily normal or slightly increased.

Treatment. Most writers have observed that the anemia of myxedema improves under thyroid therapy. Lerman and Means¹⁴ conclude that thyroid extract alone is sufficient to cause the anemia to disappear slowly, but that iron, in addition to the thyroid extract, accelerated regeneration of the blood if hypochromia persists, and that liver extract is given in those cases with a blood picture of pernicious anemia.

Our experience, both clinically and experimentally, has led us to believe that neither liver extract nor iron, alone or in combination, is of any real value in treating the anemia of myxedema. It has been

noted that intensive intramuscular liver extract failed to cause any reticulocyte response in either Case 1 or 2. Also, in spite of adequate doses of iron, Case 3 developed his anemia while under observation. Only in Case 5 who had a definite hypochromia did iron seem indicated and which probably accelerated blood formation. In each case, thyroid extract stimulated hemapoiesis with improvement in the blood, though we have been impressed with the slowness of the process.

These clinical observations are directly comparable to the experimental findings that we observed in myxedematous rabbits, *i. e.*, a definite reticulocyte response of 8 to 14% on the fifth to seventh day following varying doses of thyroid medication, with a later, slow, but sustained rise in the hemoglobin and the number of red blood cells.²³ Such a response did not occur with either iron or intramuscular liver extract. Furthermore, direct experimental evidence of bone marrow stimulation by thyroid extract has been reported by Kunde *et al.*,¹² Limm *et al.*,¹⁵ Adams and Shevket,¹ and Latta and Benner.¹³

Summary. 1. The exact etiology of the anemia of myxedema is unknown, but it is probably the result of decreased blood formation, due to the hypometabolic effect on the bone marrow.

2. In addition to the usual physical signs of myxedema, the anemic patient may present such clinical features as a lemon-yellow pallor, glossitis, paresthesias, and an achlorhydria. An erroneous diagnosis of pernicious anemia may be made.

3. In 3 cases, the mean corpuscular volume and the hemoglobin content of the red blood cells showed that the anemia was normocytic and normochromic in character. In the fourth case an achlorhydria, hypochromia and microcytosis may have been due to an associated iron-deficiency anemia.

4. Though thyroid extract causes a prompt increase in the basal metabolic rate, a transient decrease in the blood count may first be noted, followed by a slow, and sustained rise in both hemoglobin and erythrocytes.

5. In the presence of hypochromia, iron may accelerate the regeneration of blood cells, but liver extract appears to be of no value in this type of anemia.

REFERENCES.

- (1.) Adams, A. E., and Shevket, F.: *Physiol. Zool.*, 2, 181, 1929. (2.) Baker, W. A.: *J. Kansas Med. Soc.*, 24, 321, 1924. (3.) Boothby, W.: *Myxedema*, Oxford Med., New York, Oxford Univ. Press, Pt. 3, 3, 942, 1932. (4.) Crotti, A.: *Thyroid and Thymus*, Philadelphia, Lea & Febiger, p. 218, 1922. (5.) Emery, E. S.: *Am. J. Med. Sci.*, 165, 577, 1923. (6.) Esser: *Deutsch. Arch. f. klin. Med.*, 89, 576, 1907. (7.) Friedländer, M., Laskey, N., and Silbert, S.: *Endocrinology*, 19, 342, 1935. (8.) Giffin, H. Z., and Bowler, J. P.: *Minnesota Med.*, 6, 13, 1923. (9.) Hasley, V.: *Brit. Med. J.*, 1, 111, 1885. (10.) Howard, C. P.: *J. Am. Med. Assn.*, 48, 1402, 1907. (11.) Hun, H., and Prudden, M.: *Am. J. Med. Sci.*, 96, 1, 1888. (12.) Kunde, M. M., Green, M. F., and Burns, G.: *Am. J. Phys.*, 99, 469, 1932. (13.) Latta, J. S., and Benner, M. C.: *Am. J. Anat.*, 54, 115, 1934. (14.) Lerman, J.,

and Means, J. H.: (a) *Endocrinology*, 16, 523, 1932; (b) *J. Clin. Invest.*, 11, 167, 1932. (15.) Limm, R. K. S., Sarkar, B. B., and Graham Brown, J. P. H.: *J. Path. and Bact.*, 25, 228, 1922. (16.) Lissner, H., and Anderson, E. M.: *Endocrinology*, 15, 365, 1931. (18.) MacKenzie, G. B.: *J. Am. Med. Assn.*, 86, 462, 1926. (18.) Marine, D., and Boas, E. P.: *Myxedema*, George Blumer's edition of Billings Forchheimer's *Therapeutics of Internal Diseases*, New York, D. Appleton & Co., 4, 130, 1924. (19.) Means, J. H., Lerman, J., and Castle, W. B.: *New England J. Med.*, 204, 243, 1931. (20.) Minot, G. R.: *Med. Clin. North America*, 4, 1733, 1921. (21.) Orr, J. W.: *J. Path. and Bact.*, 39, 503, 1934. (22.) Pitfield, R. L.: *Am. J. Med. Sci.*, 151, 409, 1916. (23.) Sharpe, J. C., and Bisgard, J. D.: (a) *J. Lab. and Clin. Med.*; (b) *The Anemia of Myxedema* (to be published). (24.) Stone, C.: *Ann. Int. Med.*, 2, 215, 1928. (25.) Sturgis, C. C.: *Med. Clin. North America*, 5, 1251, 1922. (26.) Thompson, W. O.: *J. Clin. Invest.*, 2, 477, 1926. (27.) Warfield, L. M., and Greene, I. W.: *J. Michigan State Med. Soc.*, 24, 79, 1925. (28.) White, W. H.: *Lancet*, 1, 154, 1913.

THE SEDIMENTATION RATE IN ANGINA PECTORIS AND CORONARY THROMBOSIS.*

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THE erythrocyte sedimentation rate has been found elevated in coronary thrombosis,⁹ and it has been suggested that this finding may be of value in diagnosis, prognosis and treatment. The present communication presents a comparison of the rate of red blood cell sedimentation in cardiac infarction and angina pectoris. The purpose is to ascertain the value of the test and to obtain further information concerning the underlying pathologic processes.

Methods. The erythrocyte sedimentation rates were determined according to the method of Rourke and Ernstene.¹⁰ "The corrected sedimentation index," according to this method, is the maximum rate of settling of the red blood cells, corrected for the percentage volume of erythrocytes in the blood specimen; the normal for young adults lies between 0.08 and 0.35 mm. per minute. The fibrinogen content of the plasma was measured by the method of Wu;¹⁵ the serum cholesterol by the method of Ling.⁸

The patients with angina conformed to those described by Heberden.⁶ The diagnosis was confirmed in each case by observation during an attack. So far as could be determined, they suffered from no illness other than coronary artery disease. All patients had been observed in this clinic at weekly intervals for months or years and their clinical courses were well known.

The diagnosis in the cases of coronary thrombosis was established by the characteristic history, clinical course and changes in electrocardiographic tracings. Therapy in these cases included 3 weeks' complete bed rest in

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the hospital and whenever possible 3 additional weeks at home or in a nursing home. Blood was obtained from these patients as soon after entrance to the hospital as was feasible and once or twice a week thereafter until discharge or until the index had returned to normal. Additional tests were made in some patients several months after discharge from the hospital.

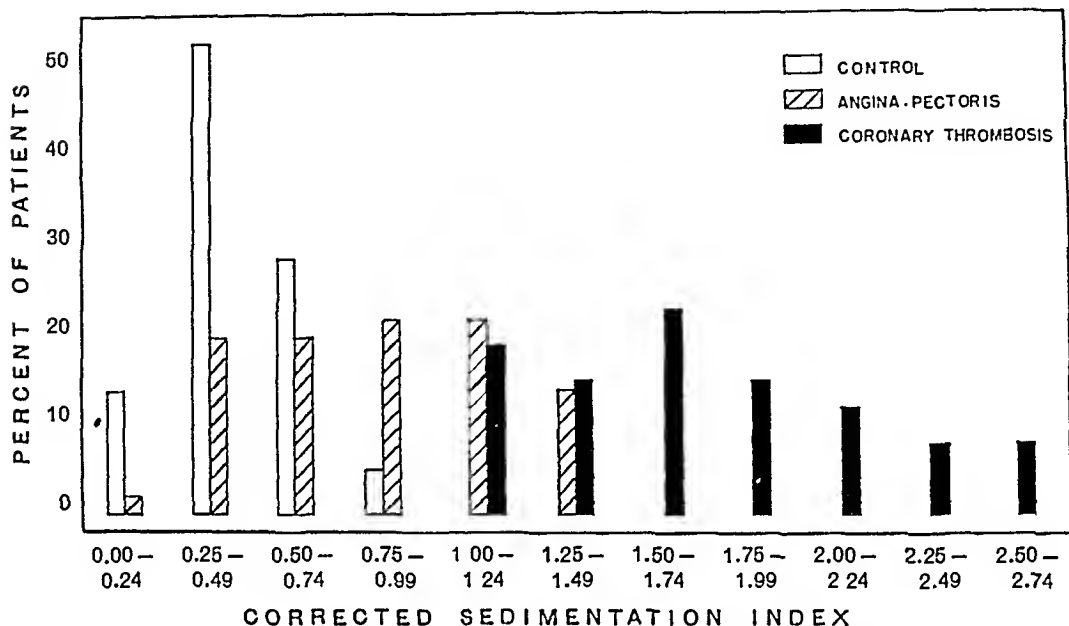


FIG. 1.—The corrected sedimentation rate in 21 healthy persons 45 to 70 years of age, 55 patients with angina pectoris and 37 patients 4 to 12 days after the onset of coronary thrombosis.

Results. Controls. It has been suggested that the sedimentation rate may be increased in old age, arteriosclerosis and hypertension.^{7,16} No figures obtained by the methods employed in this investigation are available in this group of subjects. Consequently the corrected sedimentation indices of 21 persons aged 45 to 70 were studied (Fig. 1). All these persons were working and apparently healthy, although they showed varying degrees of arteriosclerosis and several had moderate hypertension. Of these subjects, two-thirds had an index below 0.50, 1 had an index greater than 0.70, the remaining indices were 0.50 to 0.70. It is evident that individuals in this age group without evidence of disease may have sedimentation indices somewhat higher than the accepted normal for young adults; indices up to 0.70 are apparently normal.

Coronary Thrombosis. Coronary thrombosis was studied in 25 men and 12 women: 27 had a history of angina pectoris in the past; 1 patient was in the fourth decade of life, 7 were in the fifth, 16 in the sixth, 11 in the seventh and 2 were in the eighth. The sedimentation indices of 2 patients, measured within 10 hours after the onset of symptoms, were 0.95 and 1.35; the indices of three

others, measured within 24 hours of the onset of pain, were 0.53, 0.55 and 1.20.

During the first few days after the onset of an attack of coronary thrombosis, the sedimentation rate increased rapidly; 83% of the patients studied developed indices greater than 1.0 before the fourth day. The maximum increase was found between the fourth and twelfth day at which time all sedimentation indices were higher than 1.0 and 66% of the indices were greater than 1.5 (Fig. 1). After 12 days the frequency of relatively low sedimentation rates increased; after 21 days indices less than 1.0 were found in 60% of patients (Table 1).

TABLE 1.—THE SEDIMENTATION RATE IN CORONARY THROMBOSIS AT VARIOUS TIME INTERVALS AFTER THE ONSET OF SYMPTOMS.

Days after onset of symptoms.	Corrected sedimentation index.				
	0.28 to 0.49.	0.50 to 0.99.	1.00 to 1.49.	1.50 to 1.99.	2.00 to 2.60.
	Per cent of patients.				
1-4	0	17	50	25	9
5-9	0	0	30	40	30
10-14	0	20	25	45	10
15-19	5	36	36	18	5
20-24	14	48	14	14	10
25-30	33	28	19	10	10

In 13 instances the rate returned to normal (less than 0.70 mm. per minute) between 14 and 28 days after the onset of symptoms. In 19 patients the index was still elevated at the time of discharge (22 to 32 days after the onset of the disease). The remaining 5 patients died in the hospital during the acute attack (Fig. 2); these patients had indices of 1.0 to 1.75 1 to 3 days before death.

Patients with pulmonary infarction usually had a rapid sedimentation rate, but similarly increased indices were observed in patients without evidence of pulmonary complications.

Angina Pectoris. The sedimentation rate was studied in 55 patients (43 men and 12 women) with angina pectoris in whom the duration of the disease varied from 3 weeks to 10 years. Three patients were in the fourth decade of life, 8 were in the fifth, 31 in the sixth and 13 in the seventh. Approximately one-half the patients had electrocardiographic evidence of coronary artery disease, an equal number had hypertension and about one-third had cardiac enlargement by Roentgen ray.

In 21 patients the sedimentation indices were 0.70 or less; in the remainder (62%) the values were between 0.73 and 1.38 (Fig. 1). The sedimentation index tended to be 0.70 or lower in those patients whose symptoms were less than 6 months in duration. Hypertension, cardiac enlargement (Roentgen ray) electrocardiographic evidence of coronary artery disease, or a history of preceding coronary occlusion did not influence appreciably the frequency of low sedimentation indices nor was there any evidence that patients

with angina at rest tended to have higher indices than patients with angina only on exertion (Table 3).

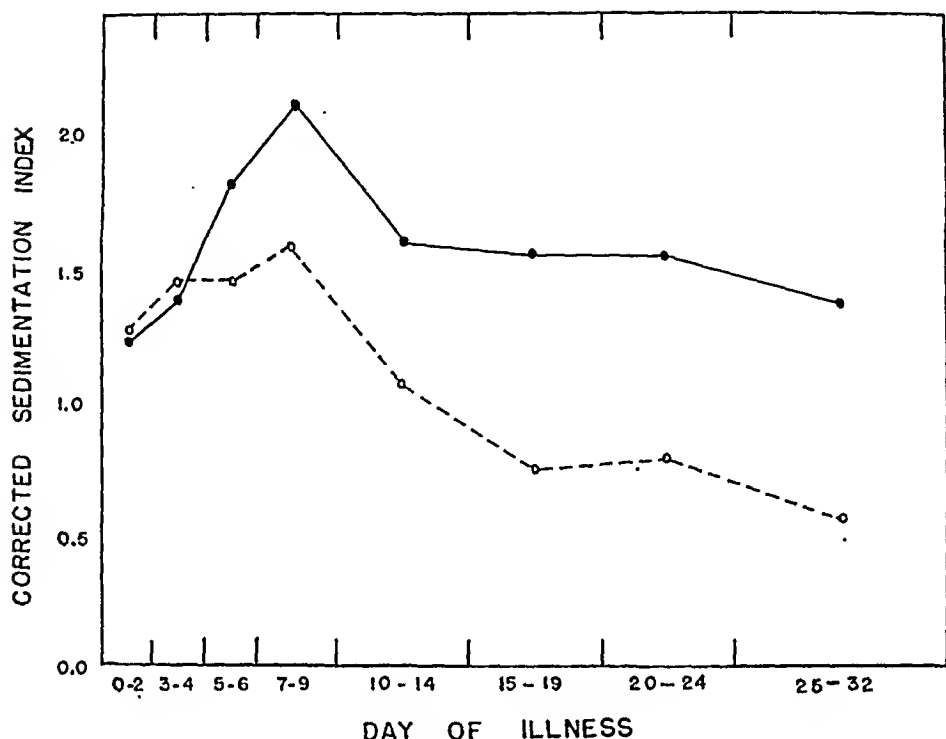


FIG. 2.—The corrected sedimentation index in coronary thrombosis. ○—○, composite curve of 13 patients whose sedimentation rates returned to normal within 4 weeks after the onset of symptoms. ●—●, composite curve of 19 patients whose sedimentation rates failed to return to normal by 28 days.

TABLE 2.—THE CORRECTED SEDIMENTATION INDEX IN 31 PATIENTS WITH CORONARY THROMBOSIS 6 TO 12 MONTHS AFTER DISCHARGE FROM THE HOSPITAL.

Corrected sedimentation index at time of discharge.	Clinical condition 6 to 12 months after discharge from hospital.		
	Dead.	Cardiac* symptoms.	No cardiac symptoms.
	Per cent of patients.		
0.28-1.00 (13 patients)	15	54	31
1.10-2.38 (18 patients)	39	39	22

* Angina pectoris, congestive failure or cardiac asthma.

In 20 patients the sedimentation rates were measured again after an interval of 1 to 26 months. In 10 instances there were increases of 0.38 to 1.76 mm. per minute (50% to 300%). Five of these patients had had a definite increase in the severity of symptoms within 2 weeks prior to the repetition of the test. Three had shown a striking decrease in symptoms during the preceding 2 weeks; the remaining 2 had shown no apparent change in clinical condition. Subsequent determinations in these patients showed a decrease of the sedimentation index toward the previous level. An eleventh

patient developed congestive failure during the period of observation; with the onset of edema there was a decrease in the sedimentation rate. Repeated determinations in the remaining 9 patients showed a change of less than 0.30 mm. per minute (33% or less). In none of these patients was there any evidence of recent change in clinical condition.

TABLE 3.—FREQUENCY OF LOW SEDIMENTATION RATES (CORRECTED SEDIMENTATION INDEX) IN PATIENTS WITH ANGINA PECTORIS.

	No. of patients studied.	Per cent of patients with C. S. I. less than 0.7.
Duration of symptoms: Less than 6 months . . .	12	75
18 months to 9 years . . .	33	33
Type of angina: Only on exertion . . .	34	41
At rest as well as on exertion . . .	21	38
Previous coronary thrombosis: No evidence in history . . .	39	45
Definite history of attack . . .	16	31
Blood pressure: Normal . . .	28	46
Hypertension . . .	26	31
Heart size (7-foot roentgenogram): No enlargement . . .	29	59
Enlargement . . .	19	31
Electrocardiogram: No evidence of coronary disease . . .	25	48
Evidence of coronary disease . . .	28	36
Serum cholesterol: 184-250 mg. per 100 cc. . .	19	31
255-413 mg. per 100 cc. . .	16	56

Comment. It is generally agreed that the rate of sedimentation of the red blood cells is increased in the presence of infection or tissue damage and is an index of the severity of the processes involved. It is to be expected, therefore, that coronary thrombosis and the resulting myocardial infarction will be accompanied by an abnormally rapid sedimentation rate. Measurements of the sedimentation rates of 58 cases of coronary thrombosis have been reported in the literature;^{1,2,7,9,12,14} the present communication adds 37 more. In every instance the sedimentation rate was abnormally rapid at some time during the course of the disease. Thus, it would appear that a rapid sedimentation rate is one of the most constant manifestations of coronary thrombosis.

In 1931, Rabinowitz, Shookhoff and Douglas⁹ suggested that the test "may be valuable in diagnosis in cases appearing for examination a number of days after an attack and presenting a normal temperature and blood count. . . . Repeat determinations . . . may aid materially in prognosis and treatment. . . . It appears advisable to keep a patient in bed for at least as long as the sedimentation time still suggests active myocardial changes." We have been unable to find any report concerning the value of the procedure in actual practice.

The test frequently helps in differentiating between coronary thrombosis and severe paroxysms of angina pectoris. This is especially true if the patient is seen for the first time several days or a week after the episode. Under such conditions it may be

impossible to ascertain whether fever, leukocytosis or changes in the electrocardiogram have taken place. A persistently normal or only slightly increased sedimentation rate between the fourth and twelfth day after the attack is strong evidence that there has been no myocardial infarction. Conversely, a marked increase in sedimentation rate, especially if the rate shows progressive changes from day to day, may be of distinct aid in establishing the diagnosis of coronary occlusion. It must be remembered, that patients with angina pectoris may show an elevated sedimentation index. This rarely reaches as high as 1.40, whereas patients with coronary occlusion usually have indices greater than 1.50. The test is, of course, of no value in differentiating between myocardial infarction and tissue damage elsewhere such as may occur in gall bladder disease.

We have found the test an aid in following the course of the disease but of little value in predicting the outcome of the acute attack. The period during which the sedimentation rate is rapid corresponds to the period when the maximum myocardial softening occurs. The period of recovery and healing of tissue damage is accompanied by a decrease in the sedimentation rate. The sedimentation indices of the 5 patients who died during the acute attack differed in no way from those of many who recovered. Those patients who were discharged from the hospital with elevated sedimentation rates, however, had a mortality more than twice as great as those who had low indices on discharge (Table 2).

It must be remembered that the underlying coronary arteriosclerosis predisposes to recurrent thrombosis. The best of management will not, therefore, eliminate a certain inevitable mortality. It would seem advisable, however, to continue bed rest until complete cicatrization of the myocardial infarct has probably taken place. The length of time necessary for this is not known. Large areas undoubtedly take longer than small ones. Regions of residual softening have been observed many weeks after the acute attack. Five weeks after the onset of symptoms 40% of our patients still showed high sedimentation rates. We have observed indices of 0.95 to 1.25 several months after discharge from the hospital. In the light of these facts it would seem advisable to continue bed rest until the sedimentation rate either returns to normal or shows no further progression towards normal.

Little is known concerning the sedimentation rate in angina pectoris. Burak² found the rate normal in 9 ambulatory cases of "severe" angina. Wood¹⁴ found normal rates in 6 cases of "angina of effort," whereas 5 cases of "angina of rest" showed a slight or moderate increase in rate. These 20 cases were studied by the Westergren method, without correction for the hematocrit. The hematocrit of approximately one-half of our patients with angina was greater than the average normal. This increase in hematocrit,

although slight, tends to diminish the total fall in the first hour for not only does it slow the rate at which the red cells settle but it also prolongs the time before obvious sedimentation begins.¹⁰ A close correlation between the corrected sedimentation index and the plasma fibrinogen content has been demonstrated in rheumatic fever³ and in a large number of other pathologic conditions.⁴ Essentially this same correlation was found in 15 of our patients with angina in whom the plasma fibrinogen was determined. Ham⁵ has observed an increased sedimentation rate in the defibrinated blood of some patients with markedly increased serum cholesterol. Approximately half of our patients with angina pectoris had a moderate elevation of the serum cholesterol level (250 to 415 mg. per 100 cc.); however, no correlation between the sedimentation rate and the serum cholesterol content was observed (Table 2).

Certain facts suggest that attacks of angina pectoris occasionally result in tissue damage. The occurrence of abnormalities in the electrocardiogram indicates that myocardial changes have taken place, and it has been demonstrated that areas of myocardial softening can occur even in the absence of occlusion of the coronary arteries.¹¹ During the first few months after the onset of angina the sedimentation rate is likely to be normal, later in the course of the disease it becomes more rapid. Sudden changes in the severity of the disease are not infrequent and such changes may be accompanied by a striking increase in the rapidity of red cell sedimentation.

It is evident that knowledge of the sedimentation rate may be of value in examining and following the course of patients with angina pectoris or coronary thrombosis. It must be remembered, that the test is not specific for these conditions and a single determination of the sedimentation rate, without knowledge of the clinical findings and without assurance that other tissue damage or infection is absent, is of little value.

Summary and Conclusions. 1. The corrected sedimentation index was studied in 113 persons: 37 with coronary thrombosis, 55 with angina pectoris, and 21 apparently normal persons between the ages of 45 and 70.

2. Elderly individuals, without any evidence of disease, may have a corrected sedimentation index slightly higher (up to 0.70) than the accepted normal for young adults.

3. A moderate elevation of the corrected sedimentation index (0.73 to 1.38) was found in over half of the patients with angina pectoris. There is reason to believe that attacks of angina pectoris occasionally result in myocardial damage.

4. An elevated sedimentation rate is one of the most constant manifestations of coronary thrombosis. The fastest rates were observed between the fourth and twelfth days after the onset of symptoms.

5. In two-thirds of the cases the rate was considerably greater

than that seen in angina pectoris; this may be of value in differentiating between angina pectoris and coronary occlusion during the first 2 weeks after the onset of an attack.

6. The sedimentation rate reflects the course of the disease and is an aid in following the progress of the patient but is of little or no aid in the prognosis of the acute attack.

7. The mortality of patients discharged from the hospital with fast sedimentation rates was twice as great during the first year after discharge as that of patients discharged with low or normal rates. It is advisable to continue bed rest until the sedimentation index either returns to normal or shows no further progression towards normal.

We wish to express our appreciation to Dorothy Rourke Gilligan for her kind interest and coöperation in these studies.

REFERENCES.

- (1.) Bickel, G., Mozer, T., and Sciclounoff, F.: *Arch. Mal de Coeur*, 28, 73, 1935.
- (2.) Burak, M.: *Wien klin. Wehnsehr.*, 47, 327, 1934. (3.) Ernstene, A. C.: *Am. J. Med. Sci.*, 180, 12, 1930. (4.) Gilligan, D. R., and Ernstene, A. C.: *Ibid.*, 187, 1, 1934. (5.) Ham, T. H.: Personal communication. (6.) Heberden, W.: *Med. Trans. Coll. Phys., London*, 2, 59, 1768. (7.) Hunt, H. F.: *J. Lab. and Clin. Med.*, 14, 1061, 1929. (8.) Ling, S. M.: *J. Biol. Chem.*, 76, 361, 1928. (9.) Rabinowitz, M., Shookhoff, C., and Douglas, A. H.: *Am. Heart J.*, 7, 52, 1931. (10.) Rourke, M. D., and Ernstene, A. C.: *J. Clin. Invest.*, 8, 545, 1930. (11.) Saphir, O., and Priest, W. S., Hamburger, W. W., and Katz, L. N.: *Am. Heart J.*, 10, 5, 762, 1935. (12.) Shookhoff, C., Douglas, A. H., and Rabinowitz, M. A.: *Ann. Int. Med.*, 9, 1101, 1936. (13.) Singer, R.: *Wien. klin. Wehnsehr.*, 47, 810, 1934. (14.) Wood, P.: *Quart. J. Med.*, 5, 1, 1936. (15.) Wu, H.: *J. Biol. Chem.*, 51, 33, 1922. (16.) Vickers, D. M., and Duryee, R.: *J. Lab. and Clin. Med.*, 18, 260, 1932.

FRACTIONATION STUDIES ON INTRINSIC FACTOR IN NORMAL HUMAN GASTRIC JUICE.

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It has been demonstrated^{105,14,17} that the incubation of liver or liver extract with normal human gastric juice or hog gastric tissue markedly increases the potency of liver or liver extract. This increase is probably the result of the interaction of the intrinsic factor of Castle² in the gastric juice or tissue with an extrinsic factor present in the liver. There is, however, a definite relation-

ship between the amounts of liver extract and gastric juice necessary to produce maximal reticulocyte responses when the combination is fed daily by mouth to patients having pernicious anemia. Near maximal responses do not follow the administration of smaller amounts than 4 gm. of liver extract (that derived from approximately 90 gm. of whole liver) even after it has been incubated with 100 cc. of gastric juice. To increase the potency of 4.5 gm. of liver extract satisfactorily, 50 or more cubic centimeters of gastric juice are required.^{7b}

We have previously recorded a few of the properties of the intrinsic factor in normal human gastric juice. This factor can be concentrated by the use of ultrafilters.^{10c} Most of the intrinsic factor is destroyed or used up during the process of concentration by vacuum distillation. The hematopoietic material in concentrated human gastric juice active on intramuscular injection, however, is formed during this process.^{7a} Our previous studies also confirmed the work of Castle and his associates² in that the intrinsic factor can be separated from the enzymes pepsin and rennin by casein precipitation. However, casein precipitation is not a satisfactory method for the removal of these enzymes in the isolation of the intrinsic factor. A small amount of the casein is dissolved in the gastric juice, thus introducing an extraneous protein. In addition, the removal of the last traces of pepsin and rennin with casein is quite difficult.

It is the purpose of this paper to record additional information on the properties of the intrinsic factor and the methods employed in attempting to obtain the intrinsic factor in a purer state. In many of the following studies the gastric juice was concentrated by ultrafiltration before any attempts were made at fractionation of the gastric juice. This was of great assistance, as many of the procedures would have been much more difficult, or even impossible, without preliminary concentration of the gastric juice.

Methods. All patients used in these studies were clinically and hematologically typical of pernicious anemia. On entering the hospital, the patients were placed on low vitamin B complex diet containing no meat, eggs, or milk. Daily red blood cell counts, hemoglobin determinations (Newcomer), and reticulocyte counts were made. During the peak of the rise the reticulocytes were counted twice daily. Control periods of 2 to 7 days preceded the institution of the test therapy. Following the administration of the test materials, all patients received either "Extralin" (Liver-Stomach Concentrate, Lilly) or liver extract by mouth.

The various fractions of gastric juice tested in these studies were brought to approximately the original volume with 0.3% HCl, and adjusted to pH 1.0 to 1.2, and the quantity of the material equivalent to the designated amounts was incubated for 2 hours with 1 vial of liver extract. These liver extract gastric juice digests were neutralized immediately before being administered to the patients at 4.30 P.M. The evening meal was served at 6.30 P.M. The digests were administered daily for 10 days except to Cases 4, 5, and 6, who received the digests for 15 days. Thi-

prolongation of treatment was due to the fact that the reticulocyte responses following treatment of the gastric juice with alcohol were markedly delayed.

The ultrafilters used were of the Bechold type described by Bronfenbrenner¹ and used previously,^{7a,10c} by us. The alcohol and acetone soluble portions of the gastric juice administered to Cases 3, 4, 6, and 7 were freed of the solvents by vacuum distillation as previously described^{7a} immediately after removal of the precipitate. Casein precipitation was carried out as described previously.^{10c} When Lloyd's reagent was added to the gastric juice, the gastric juice was stirred with a mechanical stirrer for from 15 to 30 minutes. If, after removal of Lloyd's reagent by centrifugation and filtration through paper, the gastric juice still contained rennet activity, more Lloyd's reagent was added and the procedure repeated until all rennet activity had been removed. The method^{10a} used for determining rennet activity is extremely sensitive.

Results. Morris¹² and his associates reported that the hemopoietic material in concentrated gastric juice active on intramuscular injection was dialyzable and soluble in 80% acetone and 80% alcohol. We, however, found that the intrinsic factor in normal human gastric juice after concentration by ultrafiltration would not dialyze through a cellophane sack either before or after precipitation of the gastric enzymes with casein. (See Cases 1 and 2, Table 1.) The intrinsic factor remained in the sack. Fractionation of the concentrated gastric juice by alcohol and acetone was also found to be unsatisfactory as a means of purification of the intrinsic factor. The material is at least partially soluble in alcohol and acetone (Cases 3, 4, 6, and 7a). However, a good portion of the intrinsic factor is destroyed by the alcohol and acetone or by the process of vacuum distillation during the removal of the solvents. The alcohol precipitates contained a small amount of intrinsic factor (Case 5), but not enough to produce a second reticulocyte rise in Case 7b following the slight response this patient had had to liver—gastric juice digest in which the alcohol soluble portions of the same gastric juice were used as a source of intrinsic factor.

Northrop¹³ was able to precipitate pepsin by the use of ammonium sulphate. We therefore hoped that the pepsin and rennin and mucus could be separated from the intrinsic factor by this reagent; however, the precipitate also contained the intrinsic factor. The precipitate formed by half saturation of 120 cc. of gastric juice with ammonium sulphate was redissolved in 0.3% HCl, incubated with 1 vial of liver extract, and fed daily to Case 8 (Table 2). A maximal reticulocyte response (14.5% at original red blood cell level of 2.17 million) and a satisfactory clinical improvement followed this therapy.

At the time it seemed strange that the intrinsic factor should be partially soluble in alcohol and yet be precipitated with ammonium sulphate. Dakin and West,⁴ however, have subsequently shown that the active principle in liver extract has similar solubility. Although we knew that alcohol was injurious to the intrinsic factor,

we felt it was advisable to treat the material precipitated with ammonium sulphate with 80% alcohol. It was found (Cases 9 and 10) however that the intrinsic factor, after ammonium sulphate precipitation, was insoluble in alcohol. This change in alcohol solubility could be due either to the increase in salt content of the fluid after the ammonium sulphate precipitation or to the absence in the redissolved juice of some material in the original gastric juice which held the intrinsic factor in the alcohol.

TABLE 1.—RESPONSES OF RED BLOOD CELLS, HEMOGLOBIN AND RETICULOCYTE PERCENTAGES OF JUICE FRACTIONATED BY DIALYSIS AND

Case No.	1.	1.	2.	2.	3.
Method used in fractionation of gastric juice	Dialyzed.*	Dialyzed.*	Ptt'd. with casein then dialyzed.*	Ptt'd. with casein then dialyzed.*	Ptt'd. with 80% acetone.*
Fraction of gastric juice used	Dialysate.	Undialyzed.	Dialysate.	Undialyzed.	Filtrate.
Cc. gastric juice derived from	120 cc.	120 cc.	120 cc.	120 cc.	120 cc.
Day.	R. B. C., mill. per c.mm. Hgb., % Ret., %	R. B. C., mill. per c.mm. Hgb., % Ret., %	R. B. C., mill. per c.mm. Hgb., % Ret., %	R. B. C., mill. per c.mm. Hgb., % Ret., %	R. B. C., mill. per c.mm. Hgb., % Ret., %
1	2.1 50 0.2	1.9 44 1.6	2.3 53 1.8	2.6 56 0.5	0.9 35 0.8
2	2.1 51 0.6	1.9 44 1.8	2.3 53 1.8	2.6 56 1.0	0.9 37 9.7
3	2.4 54 0.2	1.8 51 1.8	2.3 53 1.6	2.5 52 0.0	1.0 27 0.4
4	2.2 56 0.8	2.1 52 3.4	2.3 53 0.5	2.4 50 0.6	0.9 26 0.6
5	2.2 56 1.0	2.1 59 4.6	2.4 52 0.7	2.4 52 1.8	0.9 26 1.3
6	2.2 55 1.2	1.8 59 4.4	2.4 66 1.0	2.4 53 1.8	0.8 23 2.0
7	2.3 55 2.4	2.1 7.0	2.5 54 0.9	2.6 54 3.2	0.9 28 2.1
8	2.1 52 2.9	2.5 8.0	2.5 59 1.0	2.7 60 2.9	0.9 25 3.2
9	2.1 44 2.0	2.5 59 7.1	2.5 53 0.0	2.6 61 3.5	1.1 29 7.5
10	1.8 45 2.8	2.4 66 7.2	2.4 58 0.2	2.6 61 2.3	1.1 27 7.5
11	1.6	2.6 64 4.5	2.6 56 0.5	2.6 49 2.0	1.1 34 6.1
12		2.3 71 2.1			0.9 32 6.0
13					1.0 30 3.8
14					1.1 27 2.9
15					
16					
17					
18					
19					
20					
Daily therapy	Liver extract, 3 vials.		"Extralin," 12 capsules.		"Extralin," 10 capsules.
Day.					
1	2.3 71 2.1	2.5 66 3.6	2.6 49 2.0	1.1 27 2.0	
2	2.5 69 4.3	2.8 69 4.3	2.6 50 1.1	1.3 34 3.4	
3	2.8 69 2.2	2.8 69 2.2	2.4 51 2.0	1.6 37 3.0	
4	2.3 69 1.1	2.8 69 2.2	2.5 49 1.5	1.3 34 3.0	
5	2.7 72 3.1	2.7 72 3.1	2.8 53 1.0	1.5 37 6.0	
6	3.1 77 3.3	3.1 77 3.3	2.8 53 1.0	1.5 37 6.0	
7	3.3 68 2.6	3.3 68 2.6	3.0 56 2.0	1.7 45 13.2	
8	3.5 72 1.0	3.5 72 1.0	2.7 48 1.8	1.6 41 10.2	
9	2.5 1.2	2.5 1.2	2.9 51 1.1	1.5 41 14.0	
10	2.5 1.6	2.5 1.6	3.0 50 2.0	1.4 41 14.0	
11	3.3 83 1.6	3.3 83 1.6	2.9 51 1.8	1.5 52 14.8	
12	3.1 78	3.1 78	3.0 55 1.0	1.5 52 14.0	
13			2.7 48 1.4	1.6 48 13.0	
14			3.3 78 1.4	2.0 49 11.0	
15			3.2 82 0.2	2.2 50 7.6	
16				2.6 59 8.6	
17				2.7 59 6.7	
18				2.9 69 4.1	

* Gastric juice concentrated by ultrafiltration previous to fractionation.

† Newcomer method.

TABLE 2.—RESPONSES OF BLOOD OF PATIENTS HAVING PERNICIOUS ANEMIA TO LIVER EXTRACT-GASTRIC JUICE DIGESTS. GASTRIC JUICE FRACTIONATED BY ONE-HALF SATURATION WITH AMMONIUM SULPHATE.

Case No.	8.	9.	10.	11a.
Method used in fractionation of gastric juice	One-half saturation with ammonium sulphate	One-half saturation with ammonium sulphate, reprecipitated, then precipitated with alcohol.	One-half saturation with ammonium sulphate, reprecipitated, then precipitated with alcohol.	Casein adsorption + one-half saturation of supernatant fluid with ammonium sulphate.
Fraction of gastric juice used .	Precipitate.	Precipitate.	Filtrate.	Precipitate.
Cc. gastric juice derived from	120 cc.	150 cc.	150 cc.	150 cc.
Day.	R.B.C., mill. per c.mm.	R.B.C., mill. per c.mm.	R.B.C., mill. per c.mm.	R.B.C., mill. per c.mm.
	Hgb., %.	Hgb., %.	Hgb., %.	Hgb., %.
	Ret., %.	Ret., %.	Ret., %.	Ret., %.
1	2.8	1.9	1.4	1.7
2	2.1	2.2	1.3	1.7
3	2.3	1.9	1.2	1.9
4	2.0	2.3	1.6	1.7
5	2.4	2.3	1.2	2.1
6	2.5	2.4	1.3	2.1
7	2.5	2.4	1.3	2.1
8	2.7	2.1	1.5	2.1
9	2.5	2.3	1.5	2.1
10	2.4	2.8	1.4	2.1
11	2.9	2.5	2.4	2.5
12	2.7	2.7	2.4	2.5
13	3.1	2.7	2.4	2.5
14	3.1	2.7	2.4	2.5
15	3.1	2.7	2.4	2.5
16	3.8	2.7	2.4	2.7
Daily therapy	"Extralin," 12 capsules.	"Extralin," 12 capsules.	10 gm. whole liver + 80 cc. gastric juice.	"Extralin," 12 capsules.
1	3.8	2.7	1.4	2.7
2	3.3	3.0	1.2	2.8
3	3.1	2.4	1.1	2.9
4	3.6	7.1	1.3	3.0
5	3.5	2.9	1.2	2.8
6	3.5	7.4	2.1	3.1
7	3.5	3.1	1.2	3.1
8	3.3	3.1	1.6	3.1
9	3.3	2.8	1.5	3.0
10	3.4	7.3	3.0	3.6
11	3.4	7.3	1.5	3.7
12	4.0	8.2	1.6	4.0
13	3.3	7.6	1.1	3.7
14	3.3	7.6	1.1	3.7
15	3.3	7.6	1.1	3.7
16	3.3	7.6	1.1	3.7

† Newcomer method.

nium sulphate adsorbed on the casein, as it produced marked nausea when fed to Case 11. There was, however, a maximal reticulocyte response (17.7% on the eighth day with original red blood cell level of 1.70 million). The clinical response and rise in red blood cell count was very satisfactory.

The removal of pepsin and rennin from the gastric juice by precipitation with tricalcium phosphate offered the opportunity to remove these enzymes without adding any extraneous proteins. The tricalcium phosphate was prepared as described by Utkin.¹⁶ It was possible completely to remove all the rennet activity from the gastric juice by this method. However, during the removal of the last traces of this activity much of the intrinsic factor was also removed, although demonstrable amounts still remained. The response of Case 12 (Table 3), who received a liver extract gastric juice digest made with 120 cc. gastric juice from which all but 0.08 to 0.24 mg. of rennin per cc. had been removed, was greater than the response of Case 13. The digest administered to the latter patient was made with 150 cc. of gastric juice completely freed of pepsin and rennin with tricalcium phosphate.

The results obtained using casein and tricalcium phosphate suggested that if the right reagent were used, the enzymes pepsin and rennin might be satisfactorily separated from the intrinsic factor by the process of adsorption. Lloyd's reagent was selected next as a possible reagent. It was found that it was necessary to add from 10 to 15 gm. of the reagent per 100 cc. of gastric juice to completely remove the enzymes pepsin and rennin. When a liver extract gastric juice digest made with 150 cc. of gastric juice so freed from pepsin and rennin was fed daily to Case 14, a maximal reticulocyte response (33.6%) followed. A similar liver extract gastric juice digest made with 100 cc. of this pepsin- and rennin-free gastric juice, when fed for 10 days to Case 15, produced a rise in reticulocytes of only 12.8% and no rise in red blood cell count. When the amount of the pepsin- and rennin-free gastric juice used in the digest was increased to 150 cc., a second rise in reticulocytes up to 38.9% followed. There was a satisfactory rise in the red blood cell count. This response seemed maximal, but when the patient received 6 vials of liver extract per day by mouth and 6 cc. concentrated liver extract twice a week intramuscularly, a third reticulocyte rise (20.6%) was obtained (Table 4).

The intrinsic factor in the gastric juice after removal of all the peptic enzymes by adsorption with Lloyd's reagent was found to be precipitated on saturation with ammonium sulphate (Cases 16a and 16b), although considerable intrinsic factor was lost by this procedure.

In the preceding studies, unconcentrated gastric juice was treated with Lloyd's reagent; whereas, the gastric juice used in liver extract gastric juice digest fed to Case 11b was first concentrated by ultra-

filtration before it was treated with Lloyd's reagent. This procedure greatly reduced the total amount of Lloyd's reagent required to remove the pepsin and rennin. A reticulocyte response of 20.4% was obtained when this digest was fed to Case 11*b*. There, however, was a slight secondary response (6.5%) to a known potent material.

These responses indicated that from one-half to two-thirds of the intrinsic factor was lost during the adsorption of the enzymes pepsin

TABLE 3.—RESPONSE OF THE BLOOD OF PERNICIOUS ANEMIA PATIENTS TO LIVER EXTRACT-GASTRIC JUICE DIGESTS. (THE GASTRIC ENZYMES WERE REMOVED FROM GASTRIC JUICE BY ADSORPTION WITH TRICALCIUM PHOSPHATE.)

Case No.	12.			13.		
Method used in fractionation of gastric juice	Tricalcium phosphate adsorption.			Tricalcium phosphate adsorption.		
Mg. rennin per cc. filtrate	0.08 to 0.24.			0.		
Fraction of gastric juice used	Filtrate.			Filtrate.		
Cc. gastric juice derived from	120 cc.			150 cc.		
Day.	R.B.C., mill. per c.mm.	Hgb.,* %.	Ret., %.	R.B.C., mill. per c.mm.	Hgb., %.	Ret., %.
.	2.4	62	0.9	2.0	56	1.4
1	2.4	..	0.6	1.8	50	1.5
2	0.2	1.6	50	2.6
3	2.2	69	0.4	1.3	50	4.0
4	2.1	68	0.4	1.5	49	4.1
5	2.7	69	1.5	1.8	51	8.9
6	2.3	66	4.1	11.1
7	2.6	72	5.5	2.0	56	12.5
8	2.5	65	8.5	2.2	58	13.0
9	5.6	2.2	54	13.6
10	2.5	63	8.4	2.1	53	8.4
11	2.7	69	6.5	2.1	51	5.8
12	3.1	72	5.6	2.0	53	2.8
13	2.0	70	3.1			
Daily therapy	"Extralin," 12 capsules.			"Extralin," 12 capsules.		
.	3.0	70	3.1	2.0	53	2.8
1	2.8	70	2.3	6.8
2	3.0	70	2.4	2.1	52	5.7
3	2.4	2.0	56	7.4
4	3.0	72	2.6	2.0	55	9.9
5	2.7	71	1.9	2.2	57	16.5
6	3.0	77	2.2	2.2	55	23.0
7	3.3	86	4.4	2.3	56	22.5
8	3.3	82	4.5	23.0
9	3.2	80	3.2	2.8	66	15.6
10	3.5	2.6	63	10.1
11	2.6	66	13.3
12	2.6	66	13.2
13	2.9	67	10.1
14	2.8	69	10.8

* Newcomer method.

TABLE 4.—RESPONSE OF BLOOD TO LIVER EXTRACT-GASTRIC JUICE DIGESTS. GASTRIC ENZYMES REMOVED FROM GASTRIC JUICE BY ADSORPTION ON LLOYD'S REAGENT.

Case No.	11.	15.	15a.	16b.	11b.
Method used in fractionation of gastric juice	Adsorption with Lloyd's reagent.	Adsorption with Lloyd's reagent.	Adsorption with Lloyd's reagent and supernatant fluid saturated with ammonium sulphate.	Adsorption with Lloyd's reagent and supernatant fluid saturated with ammonium sulphate.	Concentrated by ultrafiltration and adsorption with Lloyd's reagent.
Fraction of gastric juice used	Filtrate.	Filtrate.	Precipitate.	Precipitate.	Filtrate.
Cc. gastric juice derived from	150 cc.	100 cc.	150 cc.	200 cc.	200 cc.
Day.	R.B.C., mill. per c.mm. %.	R.B.C., mill. per c.mm. %.	R.B.C., mill. per c.mm. %.	R.B.C., mill. per c.mm. %.	R.B.C., mill. per c.mm. %.
	Hgb., %.	Hgb., %.	Hgb., %.	Hgb., %.	Hgb., %.
	Ret., %.	Ret., %.	Ret., %.	Ret., %.	Ret., %.
1	1.4	29	1.0	2.4	1.7
2	1.3	28	1.0	2.3	1.7
3	1.4	28	1.0	2.4	1.8
4	1.1	28	0.9	2.4	1.8
5	1.3	29	1.2	2.5	1.7
6	1.6	26	1.3	2.5	1.9
7	1.4	25	1.5	2.6	2.0
8	1.5	25	1.5	2.5	2.2
9	1.8	28	1.5	2.6	2.1
10	1.9	26	1.7	3.1	2.3
11	2.0	29	1.8	3.3	2.4
12	2.3	28	1.8	3.2	2.4
13	5.1	11.2	4.5	8.1	5.3
14	8.6	8.6	4.5	8.1	5.0
Daily therapy	"Extralin," 12 capsules.	Liver extract (oral), 6 vials + liver extract, 6 cc. (intramuscularly).*	Liver extract, 3 vials.	"Extralin," 12 capsules.	
1	2.1	1.8	3.2	2.1	2.1
2	2.5	1.6	3.3	2.6	2.6
3	2.5	1.8	3.2	2.5	2.5
4	2.6	2.1	3.2	2.7	2.7
5	3.0	2.1	3.5	2.7	2.7
6	3.0	2.1	3.5	2.7	2.7
7	3.3	2.3	3.4	2.7	2.7
8	3.3	2.3	3.4	2.7	2.7
9	3.1	2.5	3.3	2.7	2.7
10	3.4	2.6	3.5	2.7	2.7
11	3.4	2.9	3.5	2.7	2.7
12	3.3	2.9	3.5	2.7	2.7

* Intramuscular liver extract administered twice weekly.

† Newcomer method.

and rennin by the Lloyd's reagent. However, by this procedure the pepsin and rennin could be completely separated from the intrinsic factor without adding any extraneous proteins. This method, therefore, appears to be quite satisfactory as a preliminary step for the further purification of the intrinsic factor.

It was felt advisable to do a few simple tests on the purified gastric juice at this time, although we realized that the intrinsic factor was far from being in a pure state. The original gastric juice showed titratable acid = 69 cc. N/10 per 100 cc., rennin =

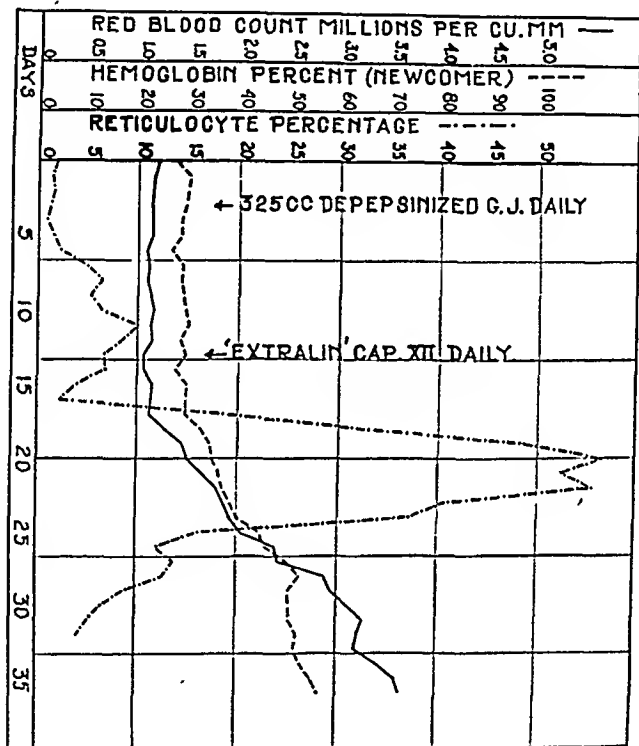


CHART I

34 mg./cc., mucous sugar = 0.175 mg./cc., and total nitrogen = 0.498 mg./cc. After the treatment of 100 cc. of gastric juice with 100 gm. of Lloyd's reagent, the titratable acid = 15 cc. N/10 per 100 cc., rennin = 0 mg./cc., mucous sugar = 0.0025 mg./cc., and nitrogen = 0.13 mg./cc. (26% of original nitrogen). The original gastric juice showed a strong biuret reaction, heat coagulable proteins, a very strong Molisch test and a weakly positive ninhydrin reaction. Precipitates were formed by 80% alcohol and half saturation with ammonium sulphate. The gastric juice, after adsorption with Lloyd's reagent, showed a questionably positive

biuret reaction, no heat-coagulable proteins, negative Molisch and negative ninhydrin reaction. There were no 80% alcohol or half saturated ammonium sulphate precipitates, although there was a slight but definite saturated ammonium sulphate precipitate, and, as shown above (Cases 16a and 16b) this precipitate contained the intrinsic factor. It is interesting that the partially purified intrinsic factor has many of the properties of the purified liver extract preparations described by Dakin and West,⁴ and Laland and Klem.¹¹

Following the completion of these studies, Greenspon⁸ reported that pepsin was antagonistic to the antipernicious anemia factor in gastric tissue, as he found that the feeding of normal gastric juice (about 250 cc. daily), peptically inactivated, was effective in pernicious anemia without the addition of beef or other source of "extrinsic factor." We had, however, previously^{10c} reported that the feeding alone of 150 cc. of gastric juice from which the enzymes pepsin and rennin had been removed by casein precipitation produced no hematologic response. Greenspon, in explaining Castle's results, concluded that the beef adsorbed the pepsin of the gastric juice and thus protected the antipernicious anemia principle. This explanation cannot apply to the increase in activity of liver extract after incubation with normal human gastric juice, as the peptic activity after incubation was as great as before. It seemed necessary, however, to repeat Greenspon's experiment. The gastric juice was collected daily from 2 normal individuals into flasks surrounded by an ice-salt mixture. It was immediately brought to pH 7.2-7.4 by the addition of strong NaOH and stored in the ice box until it was fed by stomach tube to Case 17 (Chart I) at 4.30 P.M. The average amount the patient received daily was 325 cc. Rennet activity of the juice tested just before administration averaged 4.4 mg./cc. The patient was on a meat-, egg-, and milk-free diet; and received the evening meal at 6.30 P.M. A reticulocyte peak of 10% was reached on the eighth day of treatment, but the red blood cell count showed no increase. The gastric juice in this experiment was not filtered, so the large amount of mucus and small amount of blood present in the unfiltered gastric juice might have supplied a small amount of extrinsic factor thus producing this slight reticulocytosis. This response, however, was far from maximal as a 56.5% reticulocyte rise followed the oral administration of a known potent material (Chart I).

Flood and West,⁶ Ungley and Moffett,¹⁵ Hanes, Hansen-Prüss and Edwards,⁹ Fitz-Hugh and Creskoff,⁵ and Castle and Ham³ have also reported observations at variance with Greenspon. Castle and Ham, however, concluded that incubation outside of the body of the patients should be eliminated from future studies on intrinsic and extrinsic factors, as in the presence of native pepsin and HCl a portion of the intrinsic factor is lost by this procedure. As all the studies reported here were carried out under the same condi-

tions, the destruction of intrinsic factor by the incubation (2 hours) should not interfere in comparing the activity of the various fractions of the gastric juice.

Summary and Conclusions. The daily oral administration of 325 cc. of "depepsinized" human gastric juice to a patient with pernicious anemia in relapse did not produce a satisfactory response of the blood, thus further *emphasizing the need of both an intrinsic and extrinsic factor in hematopoiesis*, as postulated by Castle and his associates.

The intrinsic factor in human gastric juice is partially soluble in 80% alcohol and 80% acetone, but it does not dialyze through cellophane, either before or after the precipitation of pepsin and rennin with casein.

One-half saturation with ammonium sulphate precipitates the intrinsic factor from normal human gastric juice and from gastric juice previously freed of pepsin and rennin by casein precipitation. This precipitate containing the intrinsic factor, however, is not soluble in 80% alcohol.

The gastric enzymes, pepsin and rennin, and the gastric mucin can be separated from the intrinsic factor by adsorption of the enzymes and mucin on tricalcium phosphate or Lloyd's reagent.

The intrinsic factor thus obtained is in a relatively pure state and no longer is precipitable on half saturation with ammonium sulphate. The saturated ammonium sulphate precipitate, however, contains the intrinsic factor.

There is considerable loss of intrinsic factor during the process of adsorption of the enzymes with tricalcium phosphate.

The loss of the intrinsic factor on Lloyd's reagent is not excessive and this procedure offers a good method for the further purification of the intrinsic factor.

REFERENCES.

- (1.) Bronfenbrenner, J. J.: J. Gen. Physiol., 10, 23, 1926. (2.) Castle, W. B.: AM. J. MED. SCI., 178, 748, 1929; Castle, W. B., et al.: Ibid., p. 764; 180, 305, 1930. (3.) Castle, W. B., and Ham, T. H.: J. Am. Med. Assn., 107, 1456, 1936. (4.) Dakin, H. D., and West, R.: J. Biol. Chem., 109, 489, 1935. (5.) Fitz-Hugh, T., Jr., and Creskoff, A. J.: AM. J. MED. SCI., 192, 168, 1936. (6.) Flood, C., and West, R.: Proc. Soc. Exp. Biol. and Med., 34, 542, 1936. (7.) Fouts, P. J., Helmer, O. M., and Zerfas, L. G.: (a) AM. J. MED. SCI., 187, 36, 1934; (b) Ann. Int. Med., 8, 790, 1935. (8.) Greenspon, E. A.: J. Am. Med. Assn., 106, 266, 1936. (9.) Hanes, F. M., Hansen-Prüss, O. C., and Edwards, J. W.: Ibid., p. 205S. (10.) Helmer, O. M., Fouts, P. J., and Zerfas, L. G.: (a) J. Clin. Invest., 11, 1129, 1932; (b) Proc. Soc. Exp. Biol. and Med., 30, 775, 1933; (c) AM. J. MED. SCI., 188, 184, 1934. (11.) Laland, P., and Klem, A.: Chem. Abstr., 30, 8278, 1936. (12.) Morris, R. S., Schiff, L., Burger, G., and Sherman, J. E.: J. Am. Med. Assn., 98, 1080, 1932; Foulger, J. H., Burger, G., Morris, R. S., and Schiff, L.: J. Med., 14, 90, 1933. (13.) Northrop, J. H.: J. Gen. Physiol., 16, 615, 1933. (14.) Reimann, F.: Med. Klin., 27, 880, 1931. (15.) Ungley, C. C., and Moffett, R.: Lancet, 1, 1232, 1936. (16.) Utkin, L.: Biochem. Ztschr., 267, 64, 1933. (17.) Walden, G. B., and Clowes, G. H. A.: Proc. Soc. Exp. Biol. and Med., 29, 873, 1932.

THE TREATMENT OF MYASTHENIA GRAVIS.

REPORT OF SIX CASES.*

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THIS report is a summary of the treatment of 6 cases of myasthenia gravis. The diagnosis was made on the history and observation of changing palsies, particularly of the extraocular muscles, and the general increased fatigability. The favorable response to the administration of prostigmin (dimethyl carbamic ester of hydroxyphenyltrimethyl ammonium methylsulphite) also proved to be of diagnostic importance. Each patient was subjected to a number of different forms of treatment in such a way as to provide a control, both in relation to the other members of the group, and to his own basic condition. In this way an attempt was made to arrive at the best therapy for each patient as an individualized problem.

The nature of myasthenia gravis and its position in the classification of diseases remain in doubt. The earliest report of myasthenia gravis of which we are aware is by Willis⁹ in "The London Practice of Physick." This description mentions the progress and changeability of symptoms throughout the day, and the predominance of symptoms referable to muscles supplied by the brain stem nuclei. Willis was of the opinion held by many subsequent authors that the condition was, at least in part, hysterical. Buzzard,⁴ in 1905, observed collections of lymphocytes in the striated muscles, and the frequent thymic enlargement. He regarded myasthenia gravis as a syndrome resulting from lymphosarcoma of the thymus with metastases to the muscles. Though his *observations* have been confirmed by others, his *interpretation* was not accepted. Norris,¹⁵ from a study of 4 autopsied cases and those in the literature, estimated that at least one-half showed gross thymic involvement. Skinner¹⁹ recorded a case in which there was gross involvement of the thymus and other lymphoid structures such as the spleen and superficial lymph nodes. Rosenow and Heilman¹⁸ regarded the myasthenic syndrome as due to a specific streptococcus. Lymphocytic infiltration though a fairly constant finding in myasthenia gravis may also be found in other diseases³; however, it is worthy

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of note that lymphorrhages are not found in the muscular dystrophies.

Metabolic studies have given no clue to the nature and etiology of myasthenia. Boothby and his collaborators¹ found no significant metabolic abnormalities after extensive study of a group of these patients.

The site of the lesion causing this syndrome has been perplexing until recently. It is of clinical importance that the visceral muscles such as the iris and myocardium are frequently affected along with somatic musculature.¹⁴ Microscopic studies of the central nervous system and peripheral nerves have yielded no demonstrable lesions. The muscle tissues are relatively normal histologically, except for the lymphorrhages which are insufficient quantitatively to account for the profound symptomatology. Physiologic study has shown that the efferent nerve conducts normally¹⁵ and that the fatigued myasthenic muscle responds to direct stimulation. This suggests that the obstruction to the passage of impulse from nerve to muscle may exist at the junction of these two structures. Since no anatomic explanation could be offered, a physiologic approach to the problem was attempted. Recently this suspicion has been strengthened by work¹³ showing that there is an area at the myoneural junction in myasthenia gravis at which impulses suffer decrement or extinction. While it can be stated with reasonable certainty that the myoneural junction is one site of physiologic disturbance, it is very likely not the only one. The observation that myasthenic symptoms are favorably influenced by ephedrine⁶ and, as shown in our case reports, by benzedrine, would indicate that other physiologic sites are implicated.

As a result of the lack of exact knowledge of the nature and seat of the primary lesions in myasthenia gravis many modes of treatment have been attempted. These varied with the concept of the underlying etiology. When the relationship to the muscular dystrophies was deemed important, the aim was to correct some possible metabolic disturbance. When the thymic aspect was stressed, treatment was directed at the thymus. With the new emphasis on the myoneural junction, drugs were employed the pharmacologic activity of which centered about this point. The following is a review of the chief modes of treatment. The results of treatment in our 6 cases are discussed. The occurrence of spontaneous remissions in the course of myasthenia gravis was fully recognized, but the prompt and lasting response to some of the agents make it appear that the relief of symptoms was not in the nature of a remission.

Treatment with Aminoacetic Acid. Remen¹⁷ thought that the metabolic disturbances in creatine-creatinine relationships which have been demonstrated for the myopathies, especially of the atrophic or pseudohypertrophic types, were likewise present in

myasthenia gravis. Aminoacetic acid (glycine, glycocoll, Glykhepar) is indicated theoretically and to a somewhat less extent empirically in the treatment of this creatine-creatinine disturbance in the myopathic dystrophies. Remen concluded, basing his opinion on one case studied, that "Glykhepar should be employed in such (myasthenic) cases." Boothby^{2a} tentatively presented a case in which glycine was tried. Others²⁰ found no benefit resulting after 5 weeks of intensive glycine therapy in myasthenia gravis.

Our own group showed no effect on symptoms with glycine in 15 gram daily doses for periods varying from 2 weeks to 3 months. Glycine was tried in 5 cases, but none showed any symptomatic change.

Physostigmine and its Analogues. In 1895 Jolly¹⁰ suggested the use of physostigmine in myasthenia, but noted that its usefulness was restricted by untoward side-reactions, such as diarrhea, excessive perspiration, and so forth. Walker²³ suggested that myasthenia gravis symptomatically resembled curare poisoning. Curare paralyzes the muscles by its action on the myoneural junction and physostigmine is its pharmacologic antagonist in this action. She found that physostigmine (and later prostigmin) had a distinctly beneficial effect on the symptoms of myasthenia. This observation has been amply confirmed by others.^{11,16,22} Everts⁷ found the oral administration of prostigmin satisfactory. Viets and Schwab²¹ suggest that the action of prostigmin in myasthenia gravis is diagnostic of that condition (a suggestion with which we are in entire accord). The following 2 brief case reports demonstrate the value of the prostigmin test in distinguishing cases which resemble myasthenia gravis:

Case Abstracts. C. A., a white man of 70, complained of difficulty in seeing. On examination he showed bilateral lid ptosis and bilateral complete external ophthalmoplegia. Both pupils were dilated and reacted poorly to light. His symptoms and signs were at a minimum in the morning and progressed as the day advanced. He showed no reaction to the administration of prostigmin in sufficient dosage for 1 week. We concluded that this was not a case of myasthenia gravis and, in the absence of clues, the diagnosis of multiple lesions of vascular origin in the midbrain was made.

Another case, L. H., a 47-year-old married woman, had *changing* extraocular palsies and difficulty with articulation and deglutition over a period of 4 years and did not respond to intramuscular or oral administration of prostigmin. Spinal fluid studies later established the diagnosis of neurosyphilis.

All of our cases were strikingly benefited by the use of prostigmin. The improvement was noted subjectively and objectively by a return to the normal state of the functions of the extraocular muscles. When the drug was withheld there was an immediate lapse toward the former state. Prostigmin was given orally and the dose individually adjusted. Each dose produced an effect lasting 1 to 4 hours. No development of tolerance to the drug has been observed.

i. e., one 15-mg. tablet is as effective after several months of prostigmin administration as at the beginning. All 6 patients finally arrived at approximately the same dosage, namely 5 to 9 15-mg. tablets evenly spaced throughout the waking day. All patients showed a weight gain varying from 5 to 25 pounds and had excellent appetites. Occasional diarrheas were controlled easily with tablets of atropine sulphate, gr. $\frac{1}{150}$, taken orally when necessary. One of our cases prior to treatment showed evidence of a marked myasthenic reaction of the myocardium which was controlled by prostigmin. The myasthenic pupillary reaction to sustained light stimulation was abolished by prostigmin. None of our cases shows a *complete* remission of symptoms, but the dose is limited by the expense of the drug and its tendency in higher quantities to produce diarrhea and sweating.

Potassium Chloride. Dale, Feldberg and Vogt⁵ demonstrated that on repeated stimulation of an efferent nerve acetylcholine is produced at the myoneural junction, except when the muscle is exhausted. Feldberg and Guimaraes⁸ showed that the administration of potassium chloride stimulates the production of acetylcholine in the structures where acetylcholine is normally produced. Function of the myoneural junction is presumed to be dependent upon the availability of acetylcholine at the junction. On the basis of these data potassium chloride has been given by mouth. Laurent and Walther¹² thought their cases were helped by potassium chloride and arrived at the conclusion that small repeated doses aid in the action of prostigmin. Wade²² finds no effects from potassium chloride.

Our series of patients showed no improvement with the use of potassium chloride either alone or as an adjuvant to some other form of treatment.

Sympathomimetic Drugs. Dr. Harriet Edgeworth¹, suffering from myasthenia gravis, accidentally discovered that ephedrine gave her considerable relief.⁶ Boothby²³ reported that 10 of 12 patients were benefited by the use of ephedrine.

Four of our 5 cases showed slight but definite improvement with ephedrine capsules, gr. $\frac{3}{4}$, taken 2 to 4 times a day. A certain unpleasant tremulousness detracted from these benefits. An attempt to find a satisfactory adjuvant to prostigmin which would be free of the undesirable effects of ephedrine led to the employment of benzedrine in the series of cases presented here. Two of the 5 cases received prostigmin alone. The other 3 received benzedrine and prostigmin and showed marked improvement. These last 3 then were treated with benzedrine alone and in only one of these was the improvement sufficient to warrant the further omission of prostigmin. In this case (No. 3), however, the continued use of benzedrine produced insomnia. It was found that a satisfactory compromise could be ensured by restricting the use of benzedrine to the early

part of the day, and then switching to prostigmin. A tendency toward wakefulness was the sole ill effect brought about by the use of benzedrine. We believe that the sympathomimetic drugs are useful as adjuvants to prostigmin in the treatment of myasthenia gravis.

Roentgen Therapy to the Thymus. Through the courtesy of Dr. Karl Kornblum and his staff all of our patients were studied roentgenographically for enlargement of the thymus, but no evidence of such enlargement was found. Nevertheless, 3 patients were given Roentgen therapy directed to the thymus, 800 r. through each of two ports. The symptoms of these 3 patients after such therapy did not show any significant change from the pretherapeutic state or from the 2 patients kept as controls.

The following is a brief summary of the 6 cases:

Case Abstracts. CASE 1.—M. B., female, aged 20, since April, 1936, has had ptosis and double vision, some difficulty with phonation and chewing, and generalized weakness. On examination there were ptoses of both upper lids, a myasthenic pupillary reaction, tachycardia, and dissociated extraocular palsies. The muscular symptoms became progressively worse as the day wore on. A hypodermic injection of one ampule of prostigmin (brown label) caused all these signs and symptoms to disappear within 3 minutes. Studies at the Graduate Hospital showed no roentgenologic evidence of enlargement of the thymus and no laboratory evidence of disturbance in blood urea nitrogen, blood calcium and phosphorus, blood urea creatine and creatinine and basal metabolic rating.

Treatment. The patient was given 15 gm. glycine every day for 6 weeks with no effect. A daily dose of 30 gm. of potassium chloride over a period of 10 days produced no change, 1600 r. of irradiation of the thymus had no effect. Ephedrine sulphate, gr. $\frac{2}{3}$ t.i.d., caused a slight improvement, but made the patient "jittery," 100 mg. mecholyl hypodermically, produced marked vagal symptoms but no amelioration of the muscular signs. Marked benefit was obtained from the oral administration of prostigmin. The average daily dose was 5 to 7 of the 15-mg. tablets. From the patient's point of view, her well-being was increased by the addition to prostigmin of 10 mg. of benzedrine twice daily. The addition of lactose tablets, identical in appearance with the benzedrine tablets, to the daily prostigmin régime had no such beneficial effect. The cardiac rate is easily controlled by the prostigmin therapy.

CASE 2.—J. B., male, aged 46, developed bilateral ptosis in 1906. A gradual progression of the symptoms ensued to the present. His condition became worse in 1918 when the patient suffered an attack of influenza. The myasthenic symptoms were minimal in the morning and increased with fatigue. Double vision, dysphagia and generalized weakness were prominent. On examination there were bilateral lid ptoses, almost complete extraocular palsy, and bilateral facial weakness of peripheral type.

Treatment. Administration of glycine, 15 gm. daily for 2 weeks, produced no change. Potassium chloride, 20 gm. daily for 1 week, exhibited a similar lack of response. Irradiation of the thymus caused no improvement. Prostigmin tablets, 5 to 8 daily, produced such marked symptomatic benefit that the patient was able to obtain a job as laborer. Ten milligrams of benzedrine in divided doses intensified the action of the prostigmin. The highest expedient dose of prostigmin failed to lift the lids completely off the pupil. A surgical operation was performed to raise the right lid and up

to the time of writing (3 months postoperative) no severe corneal complication has been observed.

CASE 3.—E. W., female, aged 39, first noticed ptosis of the left lid when reading and at night in July, 1936. Later diplopia and generalized weakness appeared. No bulbar symptoms occurred. The first examination revealed no abnormalities. At subsequent examinations ptosis and extraocular palsies were found.

Treatment. Glycine, 15 gm. daily, was used over a period of 2½ months with no benefit to the patient. Potassium chloride, 30 gm. daily, gave no relief. Ephedrine, gr. ⅓ twice daily, caused some improvement which was not noted with blank controls. Slightly better results were obtained from benzedrine, 10 mg. twice a day. Marked amelioration of symptoms was noted with prostigmin tablets, 5 to 8 per day. This patient experienced greater subjective and objective relief when a combination of prostigmin and benzedrine was used. Later the administration of 3 10-mg. benzedrine tablets alone gave best results.

CASE 4.—M. H., female, aged 23, developed in June, 1936, diplopia, speech difficulties and dysphagia. These symptoms were least incapacitating in the morning and were intensified as the day progressed. Subsequently generalized weakness and lid ptosis were noticed. Examination at various times revealed lid ptosis, changing extraocular palsies and a myasthenic pupillary reaction.

Treatment. Glycine, 15 gm. per day, was given for 1 week with no change. Potassium chloride in a daily dose of 30 gm. for 3 days produced no results. Prostigmin, 6 to 8 tablets a day, was employed with marked benefit. As an adjuvant, benzedrine has been very helpful.

CASE 5.—H. G., male, aged 35, developed in 1935 bilateral ptosis and generalized weakness. Examination in 1936 revealed bilateral ptosis and changing extraocular palsies. There was bilateral seventh nerve weakness of the peripheral type.

Treatment. Glycine, 15 gm. per day for 1 week, produced no improvement. Potassium chloride, 30 gm. daily for 1 week, evoked no response. Ephedrine and benzedrine had no effect whatsoever on this patient's symptoms. Prostigmin, 5 to 6 tablets daily, permit him to work as a laborer.

CASE 6.—L. B., a man of 61, 5 years ago complained of double vision and ptosis. These symptoms became worse as time progressed and, in addition, speech difficulties and generalized weakness became evident. He had been given large doses of glycine and vaccine therapy, but his symptoms were unrelieved. Examination revealed extraocular palsies, a myasthenic pupillary reaction, bilateral ptosis and facial palsies and soft palatal weakness. The cardiac rate was 160 and the blood pressure 190/95.

Treatment. This patient felt stronger and was able to raise both upper lids uncovering the pupils when 1 tablet of prostigmin was given every 1½ to 2 hours. As an adjuvant, benzedrine was given in 2 10-mg. doses daily. The blood pressure at present is 120/80 and the pulse rate 80 to 90. The patient is now able to pursue a routine which is almost normal.

Summary. From a review of the literature it would appear that myasthenia gravis is a disease in which there is a disturbance of the normal passage of impulse from nerve to muscle. The obstruction is probably at the myoneural junction and hypothetically may involve a faulty metabolism of acetylcholine. There may be other factors in the etiology of myasthenia gravis which have not yet been established.

Based on our limited knowledge of the cause of this disease, prostigmin is the therapeutic agent of choice. It has proved valu-

able in the treatment of all of the 6 cases reported. This therapeutic reliability has proved so dependable that the response to prostigmin has come to be employed as a diagnostic procedure. Failure of a case of suspected myasthenia gravis to respond to prostigmin casts doubt on the diagnosis. All of the 6 cases reported here gave a prompt response to prostigmin therapy, while 2 other cases with suspicious symptoms, which did not respond to the drug, were later found to have organic disease of the central nervous system. Based on the experience of others with ephedrine, benzedrine was employed so far as we know for the first time, and found advantageous in 3 of the 5 cases. The use of aminoacetic acid, potassium chloride, and Roentgen therapy produced no beneficial results.

REFERENCES.

- (1.) Adams, M., Power, M., and Boothby, W. M.: *Ann. Int. Med.*, 9, 823, 1936.
- (2.) Boothby, W.: (a) *Proc. Staff Meet., Mayo Clin.*, 7, 557, 1932; (b) *Arch. Int. Med.*, 53, 39, 1934. (3.) Butt, H. R.: *Arch. Path.*, 21, 27, 1936. (4.) Buzzard, F. E.: *Myasthenia Gravis*, Tr. Path. Soc., London, 56, 355, 1905. (5.) Dale, H. H., Feldberg, W., and Vogt, M.: *J. Physiol.*, 86, 353, 1936. (6.) Edgeworth, H.: *J. Am. Med. Assn.*, 94, 1136, 1930. (7.) Everts, W.: *Bull. Neurol. Inst., New York*, 4, 523, 1935. (8.) Feldberg, W., and Guimaraes, J.: *J. Physiol.*, 86, 306, 1936. (9.) Guthrie, L. G.: *Lancet*, 1, 330, 1903. (10.) Jolly, F.: *Berl. klin. Wchnschr.*, 32, 1, 1895. (11.) Laurent, L.: *Brit. Med. J.*, 1, 463, 1935. (12.) Laurent, L., and Walther, W.: *Lancet*, 1, 1434, 1935. (13.) Lindsley, D. B.: *Brain*, 58, 470, 1935. (14.) Markeloff, G. I.: *Arch. f. Psychiat. u. Neurol.*, 49, 482, 1912. (15.) Norris, E. H.: *Am. J. Cancer*, 27, 421, 1936. (16.) Pritchard, E. A.: *Lancet*, 1, 432, 1935. (17.) Remen, L.: *Deutsch. Ztschr. f. Nervenhe.*, 128, 66, 1932. (18.) Rosenow, E., and Heilman, F.: *Proc. Soc. Exp. Biol. and Med.*, 34, 477, 1936. (19.) Skinner, E.: *J. Neurol. and Psychopathol.*, 4, 344, 1924. (20.) Thomas, K., Milhorat, A., and Techner, F.: *Ztschr. f. physiol. Chem.*, 205, 93, 1932. (21.) Viets, H., and Schwab, R.: *New England J. Med.*, 213, 1280, 1935. (22.) Wade, H.: *Brit. Med. J.*, 1, 1099, 1936. (23.) Walker, M. B.: *Lancet*, 1, 1200, 1934.

BOOK REVIEWS AND NOTICES.

THE MEDICAL CLINICS OF NORTH AMERICA, Vol. 21, No. 2 (Boston Number—March, 1937). Pp. 642; illustrated. Philadelphia: W. B. Saunders Company, 1937.

THE 7-paper symposium on blood dyscrasias will undoubtedly attract major attention in this volume. The pedagogic method used in Dr. Hunter's "clinic" on the leukemias seems admirably adapted to the situation, though one must note with regret his contribution to the misuse of "quite." It is pleasant to note that Jackson uses the non-committal term, "Hodgkin's Disease," for that condition, rather than such confusing and unjustifiable terms as "lymphadenoma," "lymphoblastoma," "lymphogranuloma." One wonders who slipped in ascribing Otto's description of hemophilia to 1893, and why no mention of the pathology of hemophilia is made, even in a clinical journal, is a general discourse, such as this is. In the discussion of chlorosis, the nature of the condition must be inferred by the reader; one wishes that it had been stated. With considerable emphasis on treatment throughout, this number maintains the tradition and standard of this excellent publication.

E. K.

YOGA: A SCIENTIFIC EVALUATION. By KOVOOR T. BEHANAN, PH.D., Institute of Human Relations, Yale University. Pp. 270; 18 illustrations. New York: The Macmillan Company, 1937. Price, \$2.50.

THE venerable Yoga system embraces a series of postural, breathing and psychological exercises for the attainment of discipline; likewise, there is a spiritual content for those wishing to seek salvation through adherence to its complete discipline.

Its philosophic and scientific aspects are here critically interpreted by a native of India who, after being graduated with distinction from Calcutta University, studied philosophy at the University of Toronto and finally received his degree in Philosophy from Yale University. Being determined to make a scientific study of Yoga, this Hindu returned to his native country where he became an earnest student in the institute founded and conducted by the renowned Yogin, Swami Kuvalayananda. After two years, Behanan was again at Yale, this time to subject himself to a series of physiologic and psychologic experiments, the results of which are given in some detail. By reason of these exercises, Behanan attained to an emotional stability and balance not previously known to him, but he adds that the discipline in no way influenced his intellectual outlook. William James, a deep student of mental regeneration, is quoted as having written enthusiastically of the system; to him it seemed that deeper and deeper levels of moral and intellectual power were awakened. Hypnotic phenomena are unlike the mental modifications of Yoga, since the Yogin has a definite recollection of his trance experiences which are so blissful that he longs for their repetition. One learns from Yoga that in its earlier phases, certain similarities to psychoanalysis are shown, but there are definite dissimilarities: Freud is a consistent materialist, "a hard-boiled one," and he and his disciples are too one-sided and dogmatic. Freud's "depth-psychology" would not be considered deep enough by Yoga. The rapid or violent movements known in Western exercises, are against the tradition of this system; certain postures are taken and these may be held from a few minutes to a half hour; the

chapter on postures is elucidated by many excellent illustrations. There is an indispensable glossary and a most complete index. Physiologists, psychologists and psychiatrists cannot afford to neglect this scientific evaluation of Yoga. N. Y.

THE OPERATIONS OF SURGERY. VOL. II. THE ABDOMEN. By R. P. ROWLANDS, M.S. (LOND.), F.R.C.S. (ENG.), Late Surgeon to Guy's Hospital; Late Lecturer on Surgery to the Medical School, and PHILIP TURNER, B.Sc., M.S. (LOND.), F.R.C.S. (ENG.), Consulting Surgeon to Guy's Hospital; Formerly Lecturer on Surgery and Teacher of Operative Surgery to the Medical School. Pp. 1010; 514 illustrations (4 in color). Eighth Edition. Baltimore: William Wood & Co., 1937. Price, \$10.00.

THE second volume of this well-known operative surgery is concerned with operations on the abdomen and the material is presented in much the same manner as in the former editions. The text is up to date and recent literature is generously cited. Statistical tables giving the results of operations are included to provide the reader with the end results of many of the operations described. In some chapters the authors include a discussion of the commoner complications which may follow the operative procedure and they discuss methods of recognizing and avoiding them. The symptoms of the surgical lesion, the indications for operation, the preparation for operation and even the anesthesia are given in orderly fashion, with occasional illustrative cases.

The book includes not only the operations of general surgery, but also those of the urinary tract and of the female pelvic organs. At the end is appended a chapter on surgery of the lumbar sympathetics, and also some notes on the ligation of large vessels. A final chapter on some recent developments contains paragraphs on miscellaneous subjects culled from the literature of interest to the operating surgeon.

In evaluating the book, the reader is impressed by its concise and clear text, its simple yet adequate illustrations. This edition bears out the high standard of previous editions of this work. It is probably one of the best two-volume texts on operative surgery in the English language.

L. F.

MEDICAL UROLOGY. By IRVIN S. KOLL, B.S., M.D., F.A.C.S., Attending Urologist, Michael Reese Hospital. Pp. 431; 92 illustrations and 6 colored plates. St. Louis: The C. V. Mosby Company, 1937. Price, \$5.00.

A 400 page book divided into five parts and 42 chapters, touching lightly on almost every phase of Urology, so that its reading is more of a bird's-eye view of the subject, than a book for reference. It is easy and pleasant reading, with many lengthy quotations from selected authorities. The illustrations are well chosen and reproduced. There is good advice on hematuria and pyuria, on the neglected field of endoscopy, and emphasis on when to consult a specialist.

A. R.

THE SPECTACLE OF A MAN. By JOHN COIGNARD. Pp. 252. New York: William Morrow & Co., Inc., 1937. Price \$2.50.

THIS story, partly fact and partly fancy, is told under a pseudonym by a physician who for years has practised psychoanalysis. Harvesting, a young man with a pronounced mother fixation, met a divorcee; soon they went into executive session which became their habit. At the solicitation of a woman

of easy virtue, they went to her apartment where there was a solitary contact. After some time Harvesting became acquainted with a young lady who neither made nor accepted improper advances and the book ends with their mutual affections deepening. In the meantime, by reason of warring complexes engendered in the unconscious, Harvesting sought help of the analyst to whom his innermost thoughts, actions and dreams were revealed; there is no mincing of words. Four women influenced his life—two sexually. After many analytical months, he was tranquil and emotionally stable. One wonders if women may not have contributed the more to Harvesting's adjustment and adult understanding. N. Y.

HANDBOOK OF MICROSCOPICAL TECHNIQUE. For Workers in Animal and Plant Tissues. Edited by C. E. McCLUNG, PH.D., Professor of Zoölogy and Director, Zoölogical Laboratory, University of Pennsylvania. Thirty-four Contributors. Pp. 698; 82 illustrations. New York: Paul B. Hoeber, Inc., 1937. Price, \$8.00.

THE general arrangement of the subject matter of this book is the same as in the first edition, but many chapters have been revised and enlarged. The list of contributors to this edition has been increased by 10 new names. Among additions to the book are sections on the dioxane method; on micro-injection and micromanipulation; on newer hematologic and neurohistologic technique; on the fused quartz rod for illuminating living tissue; on the centrifuge microscope and on fluorescent microscopy. The book is increased by some 200 pages, the paper is of better quality than that of the first edition; the type is more easily read, and the illustrations are clearer. To quote from the review of the first edition that was published in this journal (177, 861, 1929) "It is difficult to see how it can be omitted from the book-shelf of any biological laboratory or student earnestly connected with these subjects." H. R.

WHY WE DO IT. An Elementary Discussion of Human Conduct and Related Physiology. By EDWARD C. MASON, M.D., PH.D., F.A.C.P., Professor of Physiology, University of Oklahoma School of Medicine, Oklahoma City. Pp. 177; 5 illustrations. St. Louis: The C. V. Mosby Company, 1937. Price, \$1.50.

IN this little volume, designed for parents and teachers, more than two pages are given to classification of the psychoses. Of endocrines it is stated, "they greatly modify and they may completely control psychic function and development." Comparatively, there are more than 9 times as many murders here as in England, yet Englishmen's glands are just like ours. The attempt to cover much territory leaves relevant subjects without proper consideration. N. Y.

DIABETES. A MODERN MANUAL. By ANTHONY M. SINDONI, JR., M.D., Chief of the Diseases of Metabolism at the St. Agnes Hospital; Chief Consultant in the Diseases of Metabolism at the Oncologic Hospital, etc. Pp. 240. New York: McGraw-Hill Book Company, Inc., 1937. Price, \$2.00.

WITH the increased use of diabetic manuals by patients, physicians are steadily improving the presentation of this type of therapeutic education. Dr. Sindoni's book illustrates this trend. The Reviewer agrees with the laudatory foreword and regards this manual as one of the best that has been produced. F. L.

AUTOPSY DIAGNOSIS AND TECHNIQUE. A Manual for Medical Students, Practitioners, Pathologists and Coroners' Physicians. By OTTO SAPHIR, M.D., Chairman, Nelson Morris Institute for Medical Research; Pathologist, Michael Reese Hospital; Associate Professor of Pathology, University of Illinois Medical School, Chicago. Foreword by LUDVIG HEKTOEN, M.D. Pp. 342; 65 illustrations. New York: Paul B. Hoeber, Inc., 1937. Price, \$5.00.

THIS outline of autopsy technique and diagnosis of the lesions seen at autopsy is not at all intended to replace the textbook of pathology, but rather to aid the medical student, the intern on laboratory service and the general practitioner forced by circumstance to perform an autopsy. It describes a modified Rokitansky technique, using either a Y or straight line body incision and removes the organs *en masse*. The valuable information to be obtained from external inspection is stressed and useful tables are adjoined. The heart is opened while still attached to the lungs. Medico-legal aspects are included; its 4 pages on sudden death will be a helpful guide to many. Following a statement as to the order of examination, anatomical details are given about the relations of each organ and then notes about the lesions that one may find in it. Histologic details are purposely omitted. This authoritative statement, in the words of Hektoen's Foreword, "tells competently how to make autopsies and how to study their revelations."

E. K.

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THE CHEMISTRY OF NATURAL PRODUCTS RELATED TO PHENANTHRENE. By L. F. FIESER, Associate Professor of Chemistry, Harvard University. Pp. 456. Second edition, with an appendix. New York: Reinhold Publishing Corporation, 1937. Price, \$7.00.

THE first edition of this excellent monograph on the chemistry and biological significance of sterol compounds was reviewed and highly recommended in this Journal (192, 713, 1936). The edition was quickly exhausted. In the meantime, research in the field, which embraces the antirachitic vitamins, bile acids, sex hormones, cardiac stimulants and carcinogenic compounds, has continued at a most rapid pace.

Since the details of structural chemistry are still far from settled, it appeared to Dr. Fieser unwise for the present to revise the material so well presented in the first edition. On the other hand, during the year 1936, some 300 papers of interest in phenanthrene chemistry were published. This newer work is adequately discussed in an appendix of some 90 pages, which is included in the new edition. The index, of course, has been revised appropriately.

The appendix and revised index may be purchased separately for \$1.00. This is an excellent idea for the accommodation of the readers who have purchased the first edition. As before, the Reviewer has only the highest praise for this work.

D. D.

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THE AVITAMINOSES. The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases. By WALTER H. EDDY, PH.D., Professor of Physiological Chemistry, Teachers College, Columbia University, and GILBERT DALLDORF, M.D., Pathologist to the Grasslands and Northern Westchester Hospitals, Westchester County, N. Y. Pp. 338; 3 illustrations and 27 plates. Baltimore: The Williams & Wilkins Company, 1937. Price, \$4.50.

THIS book which is directly derived from an earlier work of the senior author is, as its authors describe it, "a helpful manual rather than a complete treatise." The material is well arranged and each vitamin is discussed from

the point of view of its nature, its functions, the clinical and anatomical manifestations and the subclinical forms of its deficiency. Chapters have been added on the vitamins and resistance to infection, and to blood regeneration. Dental caries as a problem of nutrition is also discussed. A section is devoted to methods of bio-assay of the vitamins, clinical tests for vitamin deficiency and tables of vitamin values of foods. E. W.

PRACTICAL EXAMINATION OF PERSONALITY AND BEHAVIOR DISORDERS. By KENNETH E. APPEL, M.D., PH.D., Sc.D., and EDWARD A. STRECKER, M.D., A.M., Sc.D. Pp. 219. New York: The Macmillan Company, 1936. Price, \$2.00.

In the field of medicine and surgery for sometime there have existed handbooks and short guides for the purpose of aiding students and similar workers in these various fields. In the field of psychiatry—considered by many to be nebulous—there has been a definite need for a similar handbook. Gathered together in this publication one finds a very complete organization of outlines, formal methods of approach, systems of examinations and other aids that will be of practical use to a beginner and to workers in associated fields. It brings the psychiatric field into focus with the general field of medicine in which it belongs. The authors do not pretend that this compilation makes clear the fundamental aspects of patients' disorders. Their intention seems definitely clear that it should be used for practical reference work in the student's early psychiatric life. A broad understanding of the various aspects of the field as a whole is obviously necessary to give early workers a fundamental basis from where they can carry further work into the specialized branch of psychiatry.

Ideally the book should be used in conjunction with supervised teaching rather than independently by the individual student. As indicated by the subtitle it includes many examination methods useful for study of psychiatric disorders in children. If the book is used by workers with an eye to accurate investigation and observation, it will be found to be a valuable tool. L. S.

DAS HORMON DES CORPUS LUTEUM (Biologie, Chemie und Klinik). By DR. ERICH FELS, Dozent für Geburtshilfe und Gynäkologie, Leiter der Abteilung für Biologie und experimentelle Chirurgie am Instituto de Maternidad de la Sociedad de Beneficencia, Buenos Aires. Pp. 169; 40 illustrations. Leipzig: Franz Deuticke, 1937. Price, Paper, M. 12; Bound, M. 14.40.

THIS is a systematically arranged review of the recent literature on the hormone of the corpus luteum, dealing with biological, chemical, and clinical aspects. The author's own investigations are briefly stated. Many good photographs illustrate tissue reactions, and a number of charts and tables illustrate data discussed. I. Z.

DIAGNOSIS AND NON-OPERATIVE TREATMENT OF THE DISEASES OF THE COLON AND RECTUM. By GOTTFALD SCHWARZ, M.D., Professor, University of Vienna; Head, X-ray Department, Kaiserin Elizabeth Hospital, Vienna, JACQUES GOLDBERGER, M.D., Consulting Physician, Carlsbad, and CHARLES CROCKER, M.D., New York, N. Y. Pp. 540; 246 illustrations and 9 colored plates. New York: Paul B. Hoeber, Inc., 1937. Price, \$10.50.

THE volume begins with excellent and well illustrated discussions of anatomy and physiology of the large bowel. Then comes a large section on the examination of the colon. In discussing procto-igmoidoscopy, the authors describe the commoner instruments and then present their own

"Deplicoptic" proctosigmoidoscope in considerable detail. This instrument has an especially designed optical system somewhat similar to a cystoscope. The tube used is small but a considerable range of vision is permitted by magnification. In the chapter on the examination of feces, the common parasites are described and illustrated. Dr. Schwarz has inserted a long section on the diagnosis of lesions of the large gut by Roentgen ray. Excellent cuts of Roentgen ray films are presented illustrating practically all of the usual and many of the rarer lesions of the colon. Individual diseases of the colon are then discussed in detail, pointing out in each case the etiology, morbid anatomy, symptomatology, diagnosis, findings on proctosigmoidoscopy and, finally, the prognosis and treatment. Diets, drugs and doses are given in detail.

The illustrations throughout the book are well produced. There are 9 pages of colored plates in which an attempt has been made to reproduce the typical proctoscopic findings in various types of colon disease. Although the plates are excellent, one would still be somewhat at a loss to make a diagnosis with no other help than these colored drawings. At the end is appended a list of references concerning the large bowel.

This monograph is an excellent addition to the literature on diseases of the colon and rectum. The authors have studiously avoided any reference to surgical treatment and have confined their efforts to diagnosis and non-surgical therapy. It should become a part of the library of all those interested in gastro-enterology and proctology. L. F.

CHRISTIAN R. HOLMES. MAN AND PHYSICIAN. By MARTIN FISCHER. Pp. 233; illustrated. Springfield, Ill.: Charles C Thomas, 1937. Price, \$4.00.

THIS is chiefly and ostensibly the story of a vigorous, successful personality told in a piquant, unconventional manner that seldom loses clearness thereby. Equally as important is the epic of the attempts to wrest an adequate general hospital for a great city from the fangs of politics and to develop the best possible medical school for his university. E. K.

THE MORPHINE HABIT. Its Painless Treatment. By G. LAUGHTON SCOTT, M.R.C.S., B.A. (OXON), Late Senior Physician, London Neurological Clinic; Late Chief Assistant, Neurological Department, Guy's Hospital. Pp. 105; Second edition. London: H. K. Lewis & Co., Ltd., 1937. Price 5s.

WHEN habitually used, morphine causes vagal tone dominance over that of the sympathetic, which condition must be retained during the slow withdrawal; to accomplish this a gradually developed, delirium-free belladonna tolerance is induced, and thereby is offered a physiological basis for the method. Doubtless the permanent value of the treatment is greatly enhanced by the scrupulous care given during convalescence. Many case reports are included but one regrets that the more extensive of these are of physicians. N. Y.

SOURCE BOOK OF ORTHOPÆDICS. By EDGAR M. BICK, M.A., M.D., Adjunct Orthopædic Surgeon, Hospital for Joint Diseases and Mt. Sinai Hospital; Attending Orthopædic Surgeon, Lutheran Hospital, etc. Pp. 376. Baltimore: The Williams & Wilkins Company, 1937. Price, \$4.00.

THIS book is an expansion of the author's similar book, issued in photographic format in 1933. (Reviewed in this Journal, 187, 126, 1934). It is not, as its title indicates, a reprint of important excerpts of contributions that mark the progress of orthopedics; but rather an attempt, in the words

of the Preface, at "a comprehensive history of orthopædic surgery from ancient times to the present day." Even the statement that its object is also to present the source material of contemporary practice requires interpretation, as what is really offered is a correlation by the author of the development of orthopedic practice with basic medical discoveries and with "ever-changing social concepts." The first quarter of the book (5 chapters) treats earlier periods chronologically. The rest of the text takes up to the Modern Period, which is here regarded as beginning with the 19th century, though some sections are perforce confined to the 20th century. After six chapters in this section, devoted to Physiology, Pathology, Surgery of Bones, Joints, Muscles, Tendons and non-operative Orthopedics. The book concludes with a chapter on the rise of orthopedic institutions and an Appendix of Orthopedic periodicals. We regret to record our opinion that the book is more "a catalogue of ships" than an entertainingly woven narrative. It could of course still be valuable as an assemblage of historical facts, which with the aid of a full subject index would make it a useful reference book. Unfortunately, however, the subject index is not full, and careless minor errors are so frequent (for instance, 11 on p. 354) that great reliance can hardly be placed on the accuracy of the text in general. The generous references at the end of each section to original and secondary sources of information constitute the book's most valuable feature.

E. K.

SYNOPSIS OF PEDIATRICS. By JOHN ZAHORSKY, A.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine. Assisted by T. S. ZAHORSKY, B.S., M.D., Instructor in Pediatrics, St. Louis University School of Medicine. Pp. 367; 80 illustrations. St. Louis: The C. V. Mosby Company, 1937. Price, \$4.00.

This is an adequate presentation of Pediatrics according to the method developed in the old Quiz Compendes. For some students and in some schools such a book might be used as an outline of the course to be amplified by the practical work and clinical lectures. The present edition has been thoroughly revised in many sections and the information brought up to date. The illustrations and plates are accurate and faithful reproductions of the conditions represented. Sections on the rarer syndromes are presented briefly in order to remove emphasis, whereas some sections on the important diseases and fundamental principles have been extended in a comprehensive way.

E. T., Jr.

HEMOPHILIA. Clinical and Genetic Aspects. (Illinois Medical and Dental Monographs, Vol. 1, No. 4.) By CARROLL LA FLEUR BIRCH, M.D., Assistant Professor of Medicine. Pp. 151; 23 plates of illustrations, 11 figures, 3 tables and 75 charts. Urbana, Ill.: University of Illinois, 1937. Price, Paper, \$2.00; Cloth, \$2.50.

This monograph is a carefully prepared analysis of 107 hemophilic clinical histories and genealogic trees from verified data collected by the author during 9 years at the Research and Educational Hospital of the University of Illinois. As a first hand study, it is a desirable supplement to the exhaustive compilations by Bulloch and Fildes in 1911, and by Schlossmann in 1930. This monograph will be welcomed by all students of hemophilia; especially noteworthy are the excellent, well-selected photographs of patients.

E. K.

TWINS. A Study of Heredity and Environment. By HORATIO H. NEWMAN, FRANK N. FREEMAN, KARL J. HOLZINGER. Pp. 369; 33 figures, 39 plates of illustrations, and 96 tables. Chicago: University of Chicago Press, 1937. Price, \$4.00.

THE contents of this book is made up of studies and observations by a biologist, a psychologist and a statistician, upon 100 pairs of twins.

The method was first to separate these twins into two groups: "identical" ("monozygous," "monochorionic," "uniovular") and "fraternal," of each of which there were 50 pairs. Second, to divide the "identical" twins into two groups: *a*, those that had grown up together, of which there were 30 pairs; and, *b*, those that had been separated in childhood and grown up under different environmental conditions, of which there were 20 pairs.

The twins were then compared with one another and the different groups with one another, using for the purpose the usual physical observations and measurements, and judging the intelligence and personality by the Stanford Revision of the Binet-Simon Test of Intelligence, the Otis Self-administered Test of Mental Ability, Stanford Achievement Test, the Downey Will-Temperament Test, the Woodworth-Mathews Questionnaire and the Tapping tests for objective determination of handedness.

After the elaborate studies were completed it was disappointing to record that no positive conclusions upon the main problem could be arrived at. It seemed that environment played a rôle in the development of personality of identical twins separated in infancy; but the questions involved in comparing the influence of inheritance and environment on intellectual and personal development were too complicated to be settled. The authors think that they have "traced out a few threads in the tangled organism we call man."

J. McF.

THE 1936 YEAR BOOK OF GENERAL MEDICINE. Edited by GEORGE F. DICK, M.D., LAWRASON BROWN, M.D., GEORGE R. MINOT, M.D., S.D., F.R.C.P. (HON.) EDIN., WILLIAM B. CASTLE, M.D., A.M., M.D. (HON.) UTRECHT, WILLIAM D. STROUD, M.D., and GEORGE B. EUSTERMAN, M.D. Pp. 848; 178 illustrations. Chicago: The Year Book Publishers, Inc., 1936. Price, \$3.00.

ONE of 9 such Year Books, this volume on General Medicine gives adequate surveys of several hundred articles grouped together under the general headings of Infectious Diseases (George F. Dick); Diseases of the Chest (Excepting the Heart) (Lawrason Brown); Diseases of the Blood and Blood-forming Organs; Diseases of the Kidney (George R. Minot) and (William B. Castle); Diseases of the Heart and Blood Vessels (William D. Stroud); Diseases of the Digestive System and of Metabolism (George B. Eusterman). The authoritative position of the 6 editors should guarantee a wise selection of material, and this is confirmed by perusal of the contents. A wise selection is of especial importance as it is obvious that only illustrative articles on the chosen topics can be treated. A page or more is devoted to each article, liberally interspersed with short editorial notes, so that a good idea can be obtained of the articles' findings and conclusions. By way of illustration, Drs. Minot and Castle start their section with 13 pages (9 articles) on General Considerations; then consider the Macrocytic Anemia (32 articles), Hypochromic Anemias (9), Hemolytic Anemias (11), Hemorrhagic Disease (10), Malignant Neutropenia and Infectious Mononucleosis (8), Leukemia (12 articles). It is obvious that careful reading of such a section would help keep the progressive physician better acquainted with recent advances in hematological fields than would a much longer time spent on perusal of original articles. The danger that he will gradually become content with the mirror rather than the substance should, however, be recognized and avoided by a judicious allotment of available reading time between digests and original articles.

E. K.

NEW BOOKS.

- Heart Failure.* By ARTHUR M. FISHBERG, M.D., Associate in Medicine, Mount Sinai Hospital, New York City. Pp. 788; 25 illustrations. Philadelphia: Lea & Febiger, 1937. Price, \$8.50.
- Legal Medicine and Toxicology.* By THOMAS A. GONZALES, M.D., Acting Chief Medical Examiner of the City of New York; Associate Professor of Forensic Medicine, New York University College of Medicine, etc., MORGAN VANCE, M.D., Assistant Medical Examiner of the City of New York; Assistant Professor of Forensic Medicine, New York University College of Medicine, etc., and MILTON HELPERN, M.D., Assistant Medical Examiner of the City of New York; Assistant Professor of Forensic Medicine, New York University College of Medicine, etc. With a Foreword by HARRISON S. MARTLAND, M.D., Chief Medical Examiner, Essex County (Newark), N. J.; Professor of Forensic Medicine, New York University College of Medicine. Pp. 754; 244 illustrations. New York: D. Appleton-Century Company, Inc., 1937. Price, \$10.00.
- Physical Diagnosis.* The Art and Technique of History Taking and Physical Examination of the Patient in Health and in Disease. By DON C. SUTTON, M.S., M.D., Associate Professor of Medicine, Northwestern University School of Medicine; Attending Physician and Chairman of the Medical Division of the Cook County Hospital, etc. Pp. 495; 298 text illustrations and 8 color plates. St. Louis: The C. V. Mosby Company, 1937. Price, \$5.00.
- The Story of Living Things.* A Short Account of the Evolution of the Biological Sciences. By CHARLES SINGER. Pp. 572; 194 illustrations. New York: Harper & Bros., 1931. Price, \$3.00.
- A Suggested Experimental Study in Poliomyelitis Prevention Involving the Combined Use of Inactivated Virus and Intranasal Tanning Agents.* By S. PESKIND, B.S., M.D. Pp. 7. Cleveland: The S. P. Mount Printing Company, 1937.
- Dextrose Therapy in Everyday Practice.* A Survey of the Literature, 1900-1936, on the Experimental and Clinical Studies Applicable to Medicine and Surgery. By E. MARTIN, Sc.D., New York. With Forewords by W. N. HAWORTH, F.R.S., Director of the Department of Chemistry, University of Birmingham (Eng.), and BERNARD FANTUS, M.D., Professor of Therapeutics, University of Illinois College of Medicine. Pp. 451; 44 illustrations including 15 full-page plates. New York: Paul B. Hoeber, Inc., 1937. Price, \$3.00.
- Pathology.* By E. B. KRUMBHAR, M.D., Professor of Pathology, University of Pennsylvania School of Medicine. Vol. XIX of Clio Medica Series. Pp. 206; 18 illustrations. New York: Paul B. Hoeber, Inc., 1937. Price, \$2.00.
- Gastroscopy.* The Endoscopic Study of Gastric Pathology. By DR. RUDOLF SCHINDLER, Associate Clinical Professor of Medicine, University of Chicago; Attending Gastroscopist, Michael Reese Hospital; Consulting Gastroscopist, Cook County Hospital, Chicago. With a Preface by DR. WALTER LINCOLN PALMER, Associate Professor of Medicine, University of Chicago. Pp. 343; 89 text illustrations and 96 color reproductions of gastroscopic observations, with legends. Chicago: The University of Chicago Press, 1937. Price, \$7.50.
- Allergy. Its Practical Application.* By J. A. RUDOLPH, M.D., Associate Clinician in Charge of the Department of Allergy, Mt. Sinai Hospital; Consultant in Allergy, Cleveland Y. M. C. A. Expressly Prepared for Physicians and Students of Medicine, Containing Practical Points Necessary for the Care of Patients with Asthma, Hay Fever, Urticaria, Eczema, and Other Allergic Conditions. Pp. 224. Philadelphia: Dorrance & Co., Inc., 1937. Price, \$3.00.

Chirurgische Indikationen. By RUDOLF NISSEN, O. Prof. D. Chirurgie, Direktor der I. Chirurgischen Klinik der Universität Istanbul. Pp. 177. Leyden: A. W. Sijthoff's Uitgeversmaatschappij, N.V., 1937. Price, Paper, Hfl. 3.50; Bound, Hfl. 4.50.

The Laboratory Diagnosis of Syphilis. The Theory, Technic, and Clinical Interpretation of the Wassermann and Flocculation Tests with Serum and Spinal Fluid. By HARRY EAGLE, M.D., Passed Assistant Surgeon, United States Public Health Service, Washington, D. C.; Lecturer in Medicine, Johns Hopkins University Medical School, etc. With a Foreword by J. EARLE MOORE, M.D., Associate in Medicine, Johns Hopkins University; Physician in Charge, Syphilis Division of the Medical Clinic, and Assistant Visiting Physician, Johns Hopkins Hospital, Baltimore. Pp. 440; 27 figures and 53 tables. St. Louis: The C. V. Mosby Company, 1937. Price, \$5.00.

Early Medieval Medicine. With Special Reference to France and Chartres. Third Series, Vol. III, Publications of the Institute of the History of Medicine, The Johns Hopkins University. (The Hideyo Noguchi Lectures.) By LOREN C. MACKINNEY, Ph.D., Professor of Medieval History, University of North Carolina. Pp. 247; illustrated. Baltimore: The Johns Hopkins Press, 1937. Price, \$2.75.

Textbook of General Physiology. By T. CUNLIFFE BARNES, D.Sc., Assistant Professor of Biology, Yale University. Pp. 554; 166 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, \$4.50 with washable cloth cover.

Synopsis of Digestive Diseases. By JOHN L. KANTOR, Ph.D., M.D., Associate in Medicine, Columbia University; Gastroenterologist and Associate Roentgenologist, Montefiore Hospital for Chronic Diseases, New York. Pp. 302; 40 illustrations. St. Louis: The C. V. Mosby Company, 1937. Price, \$3.50.

Laboratory Manual of General Physiology. By T. CUNLIFFE BARNES, D.Sc., Assistant Professor of Biology, Yale University. Pp. 116 (every other one blank, excepting Index); 9 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, \$1.00, with washable paper cover.

A Textbook of Surgical Nursing. By HENRY S. BROOKES, JR., M.D., Instructor in Clinical Surgery, Washington University School of Medicine; Surgeon to the Out-Patients, Washington University Dispensary; Assistant Surgeon to Barnes Hospital. Pp. 636; 233 illustrations. St. Louis: The C. V. Mosby Company, 1937. Price, \$3.50.

NEW EDITIONS.

The Technic of Local Anesthesia. By ARTHUR E. HERTZLER, A.M., M.D., Ph.D., LL.D., F.A.C.S., Professor of Surgery in the University of Kansas; Surgeon to the Halstead Hospital, Halstead, Kansas, etc. Pp. 284; 142 illustrations. Sixth edition. St. Louis: The C. V. Mosby Company, 1937. Price, \$5.00.

Fischerisms. Being a sheaf of sundry and divers utterances culled from the lectures of MARTIN H. FISCHER, Professor of Physiology in the University of Cincinnati. By HOWARD FABING. Pp. 47; 1 illustration. A Second and Enlarged Edition by Ray Marr. Springfield, Ill.: Charles C Thomas, 1937. (A private print for his students.) Price, \$1.50.

History of Chinese Medicine. Being a Chronicle of Medical Happenings in China from Ancient Times to the Present Period. By K. CHIMIN WONG, Licentiate of Medicine and Surgery, Hongkong, etc., and WE LIEN-TEH, M.A., M.D. (CANTON); Dr. M.Sc. (TOKIO); Hon. Litt. D. (PEKING); LL.D., Sc.D., C.P.H., Director, National Quarantine Service, etc. Pp. 906; illustrated. Second edition. Shanghai: National Quarantine Service, 1936. Price, \$9.00.

PROGRESS OF MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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MASSIVE COLLAPSE OF LUNG.

MODERN interest in the subject of massive collapse of the lung dates from the work of William Pasteur which was published from 1908 to 1914. Bradford's observations during the war stimulated further investigation and since that time there have been a great many reports from both the clinical and the experimental side. The central problem in the study of massive collapse is that of etiology, but it must be admitted that the answer to this problem is not yet certain, although a considerable amount of data bearing upon the subject has accumulated. In addition to considering the causes of massive collapse, recent investigations have been directed toward determining its incidence and defining the factors which contribute to its occurrence.

In this report only those aspects of massive collapse which have been the subject of recent investigations will be considered. For a complete consideration of the subject, together with its history, the reader is referred to the many excellent reviews on massive collapse, among which may be mentioned those of Churehill,²⁷ Scott,^{122a} Musties, Spittler and McNamee,⁹⁰ Jacobaeus,⁷³ Brunn and Brill,²² Band and Hall,⁸ Matas⁹¹ and especially, Bowen's extensive monograph.¹⁵

Definition. Acute massive collapse of lung is the sudden, complete deflation of a considerable part of one or both lungs, in the absence of any rise in intrapleural pressure such as would be caused by pneumothorax, empyema or pleural effusion. This definition has been chosen because it does not arbitrarily rule out any of the suggested causes of massive collapse but does simplify the problem by excluding a large group of cases which might better be called compression of lung.

Clinical Course. Massive collapse of lung is most frequently observed following abdominal operations. The onset of symptoms is sudden; in 80% of cases it occurs within 48 hours of the operation. In a few reported cases the onset has occurred during the operation, and in others it has been several weeks later. Pain, dyspnea, tachycardia and

cough are prominent symptoms. There is nearly always a rise in temperature to 100 to 105° F. The pulse rate is from 100 to 160, and the respiratory rate 30 or more per minute. In the typical clinical case the collapse is unilateral. The chest on the affected side is almost motionless, flat and retracted. The intercostal spaces are narrowed and the percussion note is dull. Over the area of dullness, breath sounds are usually absent, or there may be faint bronchial breathing. Vocal resonance is diminished or absent and râles are rarely heard. The cough is variable; some sputum occurs early in most cases but is never great in amount in the absence of complications.

In unilateral cases the most important diagnostic signs are those indicating a shift of the mediastinum, *e. g.*, displacement of the trachea and of the apex beat.

If the cases are divided into: 1, Acute; 2, moderately severe; and 3, latent, the above description fits Group 2. The acute type may simulate pulmonary embolism with extreme dyspnea and sometimes severe, deep retrosternal pain. A few cases have resembled cardiac infarction. However, most of Groups 1 and 2 more closely resemble pneumonia. In Group 3, the latent cases, there are no symptoms at all, and although the signs are often typical and obvious, they are only found when sought for in a routine examination.

The foregoing description is an attempt to summarize a great many somewhat divergent reports. Many of the details require further discussion. Pain is very variable. Severe pain is rare; some feeling of retrosternal discomfort or constriction is quite common; or there may be no pain at all.⁶⁶ Dyspnea is a very common symptom but cyanosis is never severe and is usually absent.⁷⁷ Some observers maintain that cough and sputum are nearly always present,²⁶ others make no mention of them. In tuberculous cases suppression of expectoration is evidently a factor in producing collapse.⁶⁶

In most cases fever of sudden onset has been noted. The absence of fever in some proven cases and in all uninfected cases of experimental collapse suggests that fever may be associated with infection, though in many cases there is no other evidence of infection.

Postoperative massive collapse is usually unilateral. Henderson⁶² states that, "as one lung collapses, atmospheric pressure inflates the other lung, hence, massive collapse is almost necessarily confined to one lung; for the collapse of one lung tends to expand the other." Nevertheless undoubted cases of bilateral massive collapse have been reported from clinical observations,^{39,96} and bilateral collapse is relatively common at autopsy.^{7,12,42b,109a} The clinical course is much the same as in unilateral collapse except that death appears to be a more common result and the diagnostic signs of mediastinal displacement are absent.

Roentgen Ray Appearance. In unilateral cases the important changes observed on Roentgen ray examination are:

1. Increased density of the involved area; 2, displacement of the heart and mediastinum toward the affected side; 3, the diaphragm on the affected side is high and the respiratory excursion is decreased; 4, the intercostal spaces are narrowed on the affected side.

This Roentgen ray picture is identical with that seen in collapse due

to a foreign body in a bronchus. The displacement of diaphragm and mediastinum is never so great in pneumonia or in pulmonary infarction.^{65,74,89}

The very great density of the shadow cast by the collapsed lung has been the subject of much speculation. Some report that the lung which collapses spontaneously, as after an operation or the inhalation of a foreign body, casts a denser and more uniform shadow than does a lung artificially compressed by a pneumothorax or consolidated by pneumonia.¹³² This difference in density is apparently due to the fact that some air remains in the compressed or pneumonic lung whereas the collapsed lung is completely airless. Van Allen, La Field and Ross¹³² have recently emphasized the diagnostic importance of the uniform "ground glass" shadow cast by the collapsed lung. It has also been suggested that the unusual density of the shadow is due to excess fluid in the collapsed lung.⁹³ For this reason the term "drowned lung" has been applied to lungs which cast this very dense Roentgen ray shadow.

Jacobaeus⁷³ has called attention to a pendulum movement of the mediastinum which may be the only positive Roentgen ray finding when collapse is slight. This consists of a shift of the heart shadow toward the collapsed side on inspiration and away from it on expiration. Dislocation of thoracic structures is seen at both inspiration and expiration in collapse, but only at inspiration in pneumonia.¹³²

Richards¹¹⁸ emphasized that in typical atelectatic bronchiectasis the collapsed lower lobe is represented by a dense triangular shadow confined to the paravertebral angle and that there is no shift of the mediastinum.

TABLE 1.—REPORTED INCIDENCE OF POSTOPERATIVE MASSIVE COLLAPSE OF LUNG.

Author.	Year.	Reference number.	No. of cases.	No. of operations.	Incidence, %.
Pasteur	1914	109d	16	2,000	0.8
Pasteur	1914	109d	32	3,559	0.9
Schringer	1921	124	7	540	1.3
Elwyn	1924	42	2	1,734	0.12
Mastics <i>et al.</i>	1927	90	32	419	7.6
Scott	1929	122b	12	2,000	0.6
Scott	1929	122b	7	2,850	0.25
(Treated with CO ₂ postop.)					
Brunn and Brill	1930	22	22	456	4.8
Foss and Kupp	1930	50	2	3,433	0.06
Fuller	1930	51	8	1,478	0.5
Sheret	1930	125	...	149 male 112 female	18.1 13.7
Brown and Debenham .	1932	21	17	812	2.1
King	1933	76c	200	7,065	2.8
Eliason and McLaughlin	1934	39	55 32	26,032 8,836	0.21 0.36
Christopher and Shaffer .	1935	26	8	12,494	0.06
Snyder	1935	128	11	1,276	0.86
Rovenstine and Taylor .	1936	119	22 partial 13 massive	7,874 ...	0.30 0.20
Watter	1936	136	5	1,455	0.34

Incidence. Postoperative Series. The majority of reports concerning the incidence of massive collapse deal only with postoperative cases. The results of these surveys are summarized in Table 1. The extreme variability of the reported incidence is very obvious. It would

appear that the incidence is low (about 0.3%) when routine histories are studied and much higher (3 to 8% or more) when collapse is carefully searched for in each patient following operation. In the latter case, many instances of lesser degrees of collapse are undoubtedly included.

Many other studies of the incidence of postoperative pulmonary complications have been reported in which all complications have been grouped together. In those cases where an attempt has been made to distinguish the various complications, the percentage of complications which have been classed as collapse has varied from zero to 70%. A recent editorial³⁸ states that, "It appears reasonable to assume from the mass of accumulated evidence that atelectasis is the predominant postoperative pulmonary complication."

Mortality. It is generally agreed that the mortality in clinical cases of massive collapse is low. Scott^{122a} collected 40 cases in the literature with no deaths. Many fatal cases have since been reported but apparently no detailed investigation of the importance of massive collapse as a cause of death has been made.

Autopsy Series. In view of the low mortality seen in clinically recognized cases of massive collapse, it is not surprising that there are few reports of the incidence of collapse in routine autopsies. However, consideration of the available data indicates that massive collapse is much more common at autopsy than the clinical reports would suggest. Pasteur^{109a} found 2 cases of massive collapse in 55 successive autopsies on surgical cases. A review of the autopsy reports in the Department of Pathology, University of Toronto (1926-35), shows that there were 23 cases of massive collapse in 3346 autopsies in the past 9 years. There were, in addition, many cases listed as partial collapse.

Incidence in Other Conditions. Hemoptysis. Massive collapse frequently follows hemoptysis. Mindline⁹⁸ has reviewed the reported cases. Jacobaeus⁷³ emphasized the fact that collapse is most likely to follow a large hemorrhage in a relatively normal lung. Most of the cases occur in tuberculous patients but exceptions to this rule have been reported.⁶¹

Tuberculosis. The rôle of collapse in the course of pulmonary tuberculosis is attracting an increasing amount of attention. In addition to the cases seen following hemoptysis, many cases of acute massive collapse have been described in tuberculous patients.^{52,54,129} It is in these cases that pneumothorax has been most successfully applied in treatment.^{43,54,129} Chronic collapse⁸⁴ is probably much more common and of greater importance in influencing the course of the disease. Coryllos^{30b} regarded collapse as a constant complication of pulmonary tuberculosis. It is generally agreed that collapse exerts a very beneficial influence on the progress of lesions in the collapsed area. This is thought to be due partly to rest and partly to a lowering of the oxygen tension in the collapsed pulmonary tissue.^{2,3,30b,71} Cavities which are not in the collapsed area are probably enlarged by the greatly increased negative pressure in the thorax.

Pneumonia. The occurrence of massive collapse as a complication of pneumonia has been frequently reported.^{23b,24,32,45,71,90} The view that pneumonia is to be regarded as "an infectious (generally pneumococcal) lobar atelectasis of the lung" has been ably championed by Coryllos and Birnbaum.^{14,30c,51c,c} A discussion of the evidence for and against this

view would be out of place here, but it certainly merits careful consideration. If the view proves to be correct, the importance of collapse in pulmonary lesions will be greatly increased.

The relationship of collapse to bronchiectasis is not clear but the two are not infrequently associated.^{16,134,135}

Massive collapse has also been reported as a complication of diphtheria,^{109a} poliomyelitis, meningitis, bronchitis, child birth,¹³⁸ minor injuries, and many debilitating diseases. Its occurrence in cases of asthma will be discussed later.

Factors Affecting Incidence. *Age.* In the 40 cases collected by Scott,^{122a} the ages ranged from 12 to 49 years with 40% in the third decade. Eliason and McLaughlin³⁹ found all ages from 10 to 70 in their series with 19 out of 32 cases between 20 and 40. Watter¹³⁶ stated that the incidence of postoperative pulmonary complications in general is proportional to the age of the patient. Others feel that young adults are more liable to collapse.

Sex. In the autopsy series previously mentioned there were 13 men and 10 women. This preponderance of males is generally found. King (see Metcalf⁹⁴) found 38 males in a series of 55 cases, a greater preponderance of males than was found among postoperative pulmonary complications in general. The incidence of collapse in Sheret's¹²⁵ series is definitely higher in men. Eliason and McLaughlin³⁹ found 23 out of 32 cases in men. The difference in incidence has been attributed to the greater effect of pain on the abdominal breather, to which class most men belong.

Infection. 1. *Preëxisting Upper Respiratory Infection.* The importance of preëxisting upper respiratory infections in the causation of postoperative pulmonary complications is emphasized by several authors. Elliott and Dingley,⁴⁰ in 1914, noted that all their cases of massive collapse showed fever and mucopurulent sputum before the onset of collapse. Sise¹²⁶ found pre-operative respiratory infection in 29% of cases subsequently developing respiratory complications. Sutcliffe and Steele¹³⁰ have recently reviewed the subject from a bacteriologic viewpoint and conclude that the presence of pathogenic bacteria in the upper respiratory tract does predispose to postoperative pulmonary complications. In an examination of material aspirated from the trachea during anesthesia, Coryllos^{30c} found pneumococci in 72% of all cases examined and in 100% of cases which developed postoperative complications. The incidence of massive collapse probably increases along with that of other respiratory complications during the late winter and early spring.⁵³ This may be related to the increase of respiratory infections at that season.¹¹⁹

King,^{76b} in an extensive study of postoperative pulmonary complications, concluded that season and pre-operative respiratory infection play a minor rôle in the production of complications.

2. *Infection at the Site of Operation.* The importance of infection at the site of operation in increasing the incidence of postoperative pulmonary complications in general has been pointed out by several workers.^{33,120} It is strikingly shown in a series of cases reported by King^{76b} in which the incidence of pulmonary complications following simple appendectomy was 6.6% while after appendectomy with abscess formation it was 22.5%.

Site of Operation. Considerable attention has been given to the effect of the site of operation on the incidence of postoperative pulmonary complications.^{21,55,76c,119,126} From these papers it may be concluded that complications are much more common after abdominal operations than after any other type and that upper abdominal operations are more likely to be followed by complications, including massive collapse, than are lower abdominal operations. It is interesting that Pasteur^{109b} concluded, from his postoperative series, that massive collapse is more likely to follow operations on the lower abdomen. A similar incidence was noted in the autopsy series where 9 of the 14 postoperative deaths followed lower abdominal operations, one followed a gastrectomy and the remaining 4 were after extra-abdominal operations.

Pasteur originally believed that the collapse was almost invariably on the side of the operation. This observation has not been confirmed. In the great majority of clinical cases the collapse has been unilateral but not necessarily on the side of the operation. In the autopsy series 17 out of 23 cases were bilateral.

In a recent review of the occurrence of pulmonary collapse following thoracoplasty, Holst, Semb and Frimann-Dahl⁶⁶ found collapse following 51 of 112 operations. In 104 of these cases postoperative Roentgen rays were taken. Since many of the cases were symptomless the incidence would have been much lower if routine Roentgen ray examinations had not been made. In every case the collapse was on the side of the operation. Lambert and Berry⁷⁹ found only 6 cases of collapse in 100 patients with 152 operations; in 4 cases the collapse was on the side opposite the operation.

Anesthetic. Many recent investigations have been directed toward discovering the effect of various anesthetics upon the incidence of pulmonary complications in general rather than massive collapse in particular. Without discussing these papers in detail it may be concluded that different anesthetic agents given under similar conditions give rise to approximately the same number of pulmonary complications. Brown and Debenham²¹ found respiratory complications 4.29 times as common after spinal as after inhalation anesthetics. Sise,¹²⁶ King^{76b} and Rovenstine and Taylor¹¹⁹ failed to find this difference. The latter authors point out the rapid increase in the incidence of complications as the anesthesia is prolonged.

Pre-medication. Dawkins³⁵ has recently presented evidence for the idea that basal narcosis increases the incidence of postoperative pulmonary complications. Faulkner and Faulkner^{45a} have also emphasized the need for rapid recovery from the anesthetic so that the patient can cough up any excess secretion. It is generally agreed that the excessive use of morphine should be avoided. However, small doses probably aid normal respiration by relieving pain, and may even aid bronchial contraction.^{23a}

There is considerable disagreement concerning the use of atropine. It seems probable that it should be given pre-operatively, if there is no cough or sputum, to prevent excessive secretion. In the presence of sputum or excessive bronchial secretion, before or after operation, atropine may lead to bronchial occlusion by increasing the viscosity of the secretion.

General Condition of Patient. Rovenstine and Taylor¹¹⁹ have tabulated the incidence of postoperative pulmonary complications according to the estimated anesthetic risk. The increase in incidence in those classed as C, D or DD risks is very great.

It will be noted that much of the material presented in the foregoing sections deals with postoperative respiratory complications in general rather than with massive collapse in particular. Unfortunately, similar data on collapse do not seem to be available.

Allergy. Considerable attention has recently been given to the possibility that postoperative respiratory complications may be of an allergic nature. Clarke²⁹ has described the occurrence of typical massive collapse as a complication of bronchial asthma. He states that at least 10% of all reported cases of massive collapse show an allergic history even when no special attention was given to that factor. Wilmer, Cobe and Lee¹³⁷ made a detailed investigation of 10 patients who had suffered from postoperative pulmonary collapse and found that all showed some definite manifestations of allergy. They felt that the uniform finding of thick, viscid sputum in cases of postoperative pulmonary complications pointed to an allergic factor. They report good results from the use of peptone for desensitization before operation. The idea that postoperative infarction and collapse are due to an anaphylactic reaction to autogenous polypeptides has recently been advanced in France.^{49b} Autohemotherapy for the prevention of postoperative pulmonary complications has been recommended.^{75,95}

Before discussing the etiology of massive collapse it is necessary to review briefly some of the recent additions to knowledge concerning the structure and function of the lung.

Pulmonary Musculature. The advent of the bronchoscope and the use of lipiodol have revolutionized the study of pulmonary movements and especially movements of the bronchi. The muscular and elastic tissue found in the lung make free movement possible. The present view is that the muscular coat of the bronchial tree extends right down to the atria⁹⁷ or to the alveoli but does not extend into the alveolar walls.^{88a,f} Sensory nerve endings are found at the junctions of the bands of bronchial muscle.⁵³ On the contrary, the elastic tissue of the lung, or arbor elastica, extends from larynx to alveoli, and is continued into the alveoli as delicate strands. In addition to the bronchial musculature, there are many fine wisps of muscle lying outside the walls of the bronchial tree. These filaments are seen in the interlobular septa, in the bronchial and vascular sheaths and in the visceral pleura. The muscle is inconspicuous at any one point but when considered in its entirety it forms an appreciable tissue element in the lung and is known as the interstitial musculature of the lung.

Bronchial Movement. The movements of the bronchial musculature during respiration may be divided into length changes, width changes and peristaltoid movements. The latter are apparently for the removal of foreign material. The other movements are seen with each respiration. On inspiration, the bronchi not only elongate but also increase in diameter. On expiration, shortening and a decrease in diameter occur.^{88a,b,f} The cause of these bronchial movements is not altogether clear. The work of Luisada^{88a,b} suggests that there is active contraction and relaxation of the bronchial muscles with each respiration.

Ellis⁴¹ has recently presented evidence to show that the bronchial movements are directly due to movements of the chest wall.

The importance of the length and width changes and peristaltoid movements in the problem of bronchial obstruction is sufficiently obvious to require no comment. The significance of the bronchial and interstitial musculature in relation to collapse of lung is much less obvious. In conditions, such as asthma, in which bronchial spasm is known to occur, emphysema, not collapse, is the usual outcome.

Histology of the Lung. Until recently, pulmonary alveoli have been regarded as sacs opening only into the bronchial tree and lined by a continuous layer of non-nucleated epithelial plates and flattened epithelial cells. Miller⁹⁷ has recently reviewed the older literature on the subject and still supports this view. Communications between adjacent alveoli were first described by Adriani in 1847. This observation has been repeated frequently in apparently normal lungs and in pneumonic lungs.^{88c,d,106} Miller concluded that these alveolar pores are not normal structures but are due to some pathologic process. Macklin^{88d} believed that they are to be regarded as "... sharply localized degenerations of the ground substance of the alveolar wall ..." and of no functional significance. The observations of Van Allen¹³¹ and his colleagues on collateral respiration strongly suggest that some communications exist between adjacent airways in the periphery of the lung.

Not only has the existence of alveolar pores been repeatedly confirmed but considerable doubt has been cast upon the existence of any continuous alveolar epithelium. At a recent conference, where the pulmonary alveolar epithelium was discussed, the majority of observers reported that they had failed to find a continuous epithelium, and none had found non-nucleated epithelial plates.^{88c} Miller⁹⁷ strongly supports the existence of a continuous alveolar epithelium.

Collateral Respiration. In a series of important papers Van Allen, Lindskog and others have developed the idea of collateral respiration.^{82a,b} They found that collapse of lung could not be produced by bronchial occlusion if the bronchus occluded supplied less than an entire lobe. Air forced into a lobular bronchus under very low pressure readily passed out other lobular bronchi in the same lobe. These observations suggested that there must be transfer of air between the lobular bronchi in the periphery of the lung. The injection of India ink and other suspensions showed that this transfer of air was through pores of microscopic size and not by diffusion through intact cellular membranes. This transfer of air from the area supplied by one lobular bronchus to that supplied by another not only serves to maintain the aëration of the lung when a lobular bronchus is occluded but also prevents local overdistention if a valvular occlusion occurs. This mechanism also provides the air necessary for an expulsive effort on coughing when a bronchus is occluded.

The existence of collateral ventilation seems to be well established, in the dog at least. The amount of air which can enter an occluded lobule is at least 10% of its normal ventilation and may be sufficient to aërate the venous blood in that part of the lung. The significance of collateral respiration in relation to pulmonary collapse will be discussed below.

The Expansion of the Lung. Under normal conditions, the lungs are subjected to two opposing sets of forces. Atmospheric pressure, acting through the bronchial tree, tends to keep the lungs expanded and in contact with the chest wall. The elasticity of the lung and the intrapleural pressure oppose this force and tend to collapse the lung. Normally the sum of pulmonary elasticity and intrapleural pressure is just less than atmospheric pressure so that the lung is kept expanded. Thus the amount by which the intrapleural pressure falls short of atmospheric pressure is a measure of the force required to stretch the lung to fill the thorax.

There are three ways in which a part of the lung can collapse. These are: 1, Increase of matter other than lung in the thorax (*c. g.*, pneumothorax, hemothorax, empyema, pleural effusion, tumors); 2, decrease in the size of the thorax due to decrease in muscle tone or localized paralysis affecting any of the respiratory muscles; 3, forceful decrease in the size of the lung: (*a*) due to absorption of air from a part of the lung that has been cut off from the outside; (*b*) due to active muscular contraction of the lung.

It is obvious that in the first and second groups the intrapleural pressure will be less negative than normal because the lung is less stretched. In the third group, part of the lung has been decreased in size so that the remaining lung has to be stretched more than normally to fill the thorax. This results in a decrease in the intrapleural pressure.

By definition all cases of massive collapse have been placed in the third class and there is good evidence, both direct and indirect, that this classification is justifiable. In all reported cases of massive collapse in which the intrapleural pressure has been measured it has been below normal.^{43,51 57,72} The lowest reported pressure is -58 cm. of water.⁸¹ Indirect evidence for this decrease in intrapleural pressure is given by the uniform finding of a shift of the mediastinum to the affected side.

The Effect of Operations upon Respiration. Since abdominal operations are the most common cause predisposing to massive collapse, a knowledge of the effects of operation upon respiration is necessary before considering the etiology of massive collapse.

By combining the observations of many workers the following picture of the patient's pulmonary condition after an abdominal operation is obtained. The mean position of the diaphragm is raised so that its tidal excursion is in the upper third of its range instead of the lower third as is usual.¹⁰³ Chest expansion decreases by about 80% and diaphragmatic excursion by 65% following upper abdominal operations.¹⁰³ These changes result in a decrease in vital capacity of 8 to 80%.^{23 24 110} Vital capacity measurements are not very reliable after operation but measurement of the subtidal volume (mid-capacity, functional residual air, etc.) which are more significant show a decrease of 20%.¹⁰ Many cases show Roentgen ray changes including haziness of lung fields, prominence of basal trunks and elevation of the diaphragm. Diminished expansion of the lung bases is said to occur in all cases after operation. Breath sounds are diminished or absent at the bases in most cases and râles are frequently heard.^{103 108}

Many factors contribute to these pulmonary changes. Pain definitely limits respiratory movements. Air in the peritoneal cavity increases the normally negative intraabdominal pressure and contributes

to the elevation of the diaphragm. Distention of the bowel may add to this effect. Henderson^{62c} has recently emphasized the importance of the general loss of muscle tone seen after operations. Decrease in tone of the respiratory muscles diminishes the size of the thorax and the extent of respiratory movements.

The vital capacity of a normal individual is reduced by 10 to 20% by merely changing from the erect to the supine position.^{19,68} If this position is maintained, deflation of the lung bases follows. Thus position probably contributes to the postoperative pulmonary changes.

The condition of the lungs described following operation has been called postoperative pulmonary sub- or hypoventilation.¹¹⁵ It is distinguished from massive collapse by the fact that the intrapleural pressure is increased, while it is always diminished in massive collapse. In addition, pulmonary subventilation is bilateral and is associated with an enlargement of the diameter of the thorax.

Etiology. Of all the suggested causes of massive collapse of lung, bronchial obstruction is the best established. Mendelssohn, in 1845, showed that complete occlusion of a bronchus resulted in collapse of the lung distal to the occlusion. Lichtheim, in 1878, showed that this collapse was due to absorption of the retained air into the blood. Elliott and Dingley⁴⁰ first clearly suggested that bronchial occlusion is essential to the production of postoperative massive collapse. The introduction of the bronchoscope has thrown much new light on the problem of bronchial obstruction in recent years. Direct observation has revealed the presence of occluding secretion in the bronchi in many cases of massive collapse.^{20,22,59,60,69,70,105,127}

The more important evidence favoring bronchial obstruction as the cause of massive collapse may be summarized thus:

1. Massive collapse has been repeatedly produced experimentally by bronchial occlusion, whether the occlusion was produced by ligation of a bronchus,^{92,131} introduction of solid foreign bodies,¹¹⁶ or tenacious bronchial secretion,^{8,80} or by cauterizing a bronchus.^{1,34} This is the *only* way in which massive collapse has been produced experimentally. Much has been learned concerning the circulatory and metabolic changes which follow the experimental collapse of a lung by bronchial occlusion.^{4,6,31b,37}

2. Massive collapse is seen clinically following occlusion of bronchi by foreign bodies, neoplasms, aneurysms, or enlarged lymph nodes. The Roentgen ray picture and clinical signs in this type of collapse may be indistinguishable from those of postoperative collapse.⁶⁹

3. Bronchoscopic observations have shown that the bronchi supplying a collapsed lobe are frequently occluded by plugs of tenacious bronchial secretion. Removal of these plugs usually results in rapid reexpansion of the collapsed lobe.

4. Collapse is commonest in the right lower lobe where secretion or aspirated material is most likely to collect. Cases with excessive bronchial secretion are very likely to develop collapse. The areas of collapse may shift with the position of the patient, suggesting a movement of exudate within the lungs.^{22c,b,35c,b}

There is some disagreement among the proponents of the bronchial obstruction theory concerning the cause of the obstruction in postoperative collapse. In cases of collapse following aspiration of a foreign

body, hemoptysis or lipiodol injection, the cause of obstruction is obvious. After operations, obstruction is most likely caused by accumulation of bronchial secretion. Several factors may contribute to the accumulation of secretion. Pulmonary subventilation, resulting in diminished movement at the lung bases, leads to deficient drainage of those regions. "Internal drainage"^{74a,b,45b,85} may bring secretion from other parts of the lung to the most dependent areas. Postoperative shock^{99,100} and vagal stimulation¹¹² may result in an increase in bronchial secretion or even some degree of pulmonary edema. At one extreme may be placed cases in which excessive interference with lung movements results in the accumulation of normal bronchial secretion. At the other extreme are cases such as hemoptysis in which an excessive amount of fluid may occlude bronchi in the presence of normal respiratory movements.

Faulkner and Faulkner^{45a} suggest that aspirated material may be an important cause of bronchial occlusion. Myerson's direct bronchoscopic observations, which showed aspiration of blood into the tracheobronchial tree in 79 out of 100 tonsillectomies, support this view.¹⁰⁴

Other suggested causes of bronchial obstruction are inflammatory edema of the bronchial mucosa, vascular changes¹²³ in bronchi, possibly analogous to angioneurotic edema,¹² and bronchial spasm.^{42,81,111} Inflammatory edema would appear to be the cause of collapse in cases of atelectatic bronchiectasis^{134,135} but has not been demonstrated in cases of acute massive collapse. There is little evidence for the occurrence of angioneurotic edema. There is no direct evidence that bronchial spasm alone can produce pulmonary collapse. In conditions associated with bronchial spasm, emphysema is more likely to occur than collapse. Recent reports of the high incidence of an allergic history¹³⁷ in patients suffering from postoperative pulmonary complications and of the occurrence of true massive collapse in asthmatics²⁹ suggest that bronchial spasm may be an important contributory cause. The work of Dixon and Brodie³⁶ shows that bronchial spasm combined with a greatly decreased ventilation (artificial respiration) may result in the rate of air entry to a lobe being less than the rate at which the blood is absorbing air from that lobe, so that the lobe slowly deflates.

Collapse of lung following bronchial obstruction might arise either from a ball-valve action of the obstructing plug so that the air is pumped out of the obstructed lung, or from absorption of the air beyond the plug into the blood stream. The possibility of the latter mechanism has been repeatedly demonstrated.^{21b,63} The impossibility of the deflation of a part of a lung by ball-valve action has been clearly proven by Lindskog and Van Allen.⁸³

The important evidence against bronchial obstruction as the cause of massive collapse is:

1. At autopsy, patent bronchi are frequently found in collapsed lung. It is suggested that the occluding plugs, in these cases, have undergone postmortem liquefaction or that the occlusion is in smaller bronchioles. Clinical findings (e. g., tubular breathing) sometimes suggest patent bronchi in collapsed lobes. In a few cases, bronchoscopic examination has failed to reveal any plugging of the bronchi.^{22,22}
2. Rose Bradford's¹⁷ observations on massive collapse following thoracic injuries are of great interest. He found that massive collapse

was a relatively common sequel to chest wounds seen during the war. The collapse might involve part of a lobe, a whole lobe, or an entire lung. In some cases, the collapse was on the side of the injury, in others on the opposite side and a few were bilateral. The most striking cases were those in which a non-penetrating wound of the thoracic wall resulted in massive collapse of the contralateral lung. Bradford feels that bronchial obstruction played no part in these cases.

3. Several cases of rapid collapse of the lung have been reported in which the apparent rate of collapse greatly exceeded that which could be due to the absorption of air.^{12,73,81b,111} In some of these cases the rapid collapse may have been due to the rapid absorption of ether vapor rather than air from the lungs. Jacobaeus⁷³ reports 4 cases in which massive pulmonary collapse developed within 10 to 15 minutes following the injection of lipiodol into normal lungs without anesthesia. He suggests that the collapse was due to bronchial spasm which expelled most of the air before occluding the bronchi. The amount of lipiodol used was apparently not enough to occlude the bronchi, and the collapse often occurred in lung areas in which there was very little lipiodol and the collapse disappeared without the expectoration of lipiodol. Mindline⁹⁸ believed that collapse following hemoptysis is due to the same cause. In all these cases it seems to be impossible to be sure that bronchial obstruction was not present, but the rapidity of collapse cannot be explained by the absorption of air. Lubin⁸⁵ suggested that very rapid collapse follows bronchial occlusion in expiration.

4. Cases of collapse following tracheotomy have been noted.¹³⁹ These would appear to be due to an actual contraction of an unusually elastic lung. There is no suggestion of bronchial obstruction.

5. The finding that the areas of collapse often do not follow lobar boundaries cannot be reconciled with the observations on collateral respiration, if the collapse is due to bronchial obstruction, unless it is supposed that the alveolar pores are often occluded.

6. Some of the clinical signs of massive collapse, such as fever, are not duplicated in experimental collapse produced by bronchial occlusion. It seems probable that the presence of infection is necessary for the production of fever and that fever is not due to the collapse of lung. However, there are many clinical cases in which the fever is the only sign of infection.

This discussion shows that the theory of bronchial obstruction as the cause of massive collapse is not entirely satisfactory, and yet there is no substitute for it.

Briseoe's¹⁹ theory that the symptoms of massive collapse are always due to an associated acute pleurisy and never to the collapse of the lung has received no support.

Embolism has never been shown to cause collapse and the two are rarely associated. It has been shown that ligation of the one pulmonary artery does result in partial deflation of the affected lung but never in a true collapse.¹⁰¹ It appears that the arterial blood pressure normally aids in maintaining the inflation of the lung. Vascular changes other than embolism have been suggested but have never been accurately defined.^{12,123}

Massive collapse, like most other conditions, has been blamed on reflex causes. It seems certain that inhibition, probably reflex in origin, of the diaphragm and other respiratory muscles is an important contributing factor. Collapse has never been produced by nerve stimulation and has been seen to occur in the denervated lung.⁴⁸

Pasteur has adhered to the opinion that decreased respiratory force is the prime cause of massive collapse. The arguments against this view are: 1, If decreased respiratory force were the cause of collapse, the intrapleural pressure would be increased when collapse occurs. It is always decreased; 2, if decreased respiratory force could cause unilateral collapse, the heart would be shifted to the side opposite the lesion. Decreased respiratory force, leading to pulmonary subventilation, is generally believed to be a most important factor in favoring accumulation of secretion, bronchial occlusion and massive collapse, but it cannot be admitted as a cause of collapse *per se*.

This discussion leaves active contraction of the lung and bronchi as the only theory to oppose that of bronchial obstruction. Recent work has shown that the lung is a very muscular organ but it has not proven that contraction of this muscle can expel the air from the lungs or even completely occlude bronchi.

Prevention of Collapse. The factors which seem to be effective in controlling the incidence of pulmonary collapse after operation can all be deduced from the causes which are known to contribute to the occurrence of collapse.

Except in emergencies, patients with upper respiratory infections should not be operated upon. Care must be taken to avoid all aspiration during the anesthetic. Recovery from the anesthetic should be rapid and postoperative sedation should be carefully controlled. Too much morphine depresses respiration and favors the accumulation of bronchial secretion. Too little morphine may result in limitation of respiratory movements by pain. Small doses of morphine may actually increase bronchial motility.^{23a}

The use of atropine has been widely discussed. At present, it is generally agreed that excessive doses of atropine make the bronchial secretion tenacious and favor occlusion. It is best used only when bronchial secretion is excessive. Pasteur^{109d} reported favorably on its use. Expectorants are often recommended to thin bronchial secretion.

Abdominal dressings should be small and loose. The patient should be rolled frequently to avoid stagnation of secretion in one part of the lung.¹²¹ Complete expansion of the lungs should be induced at least every hour by voluntary deep breathing combined with rolling or by the use of carbon dioxide.

The inhalation of carbon dioxide has been widely used for the prevention and treatment of collapse and of postoperative pulmonary complications in general. The action of carbon dioxide in increasing the rate and depth of respiration is too well known to require discussion. It has been shown experimentally that carbon dioxide causes bronchodilatation,¹⁸ an increase in mean thoracic girth and expansion¹⁹ and a decrease in intrapleural pressure. Bronchoscopic observations show that carbon dioxide inhalation produces violent movements of the tracheobronchial tree and blanching of the mucous membrane.^{20,22}

There is less reduction in vital capacity after abdominal operations if carbon dioxide is given.¹¹³

Although all these actions of carbon dioxide would appear to be beneficial in preventing postoperative pulmonary complications, opinion is divided concerning its value. The majority of workers reporting on the subject favor the use of carbon dioxide.^{22,26,44b,47,62b,87,122b,128} In most cases it is stipulated that the inhalations must be combined with postural drainage. Others^{76,120,136} find that carbon dioxide inhalations are without value for the prevention of postoperative pulmonary complications. Reports of the use of carbon dioxide in the treatment of pneumonia are very encouraging.^{56,64} In general, it would appear that the administration of carbon dioxide in amounts adequate to produce real overventilation combined with postural drainage is beneficial.

Treatment of Collapse. The measures which have been advocated for the prevention of collapse (*i. e.*, rolling, deep breathing, and carbon dioxide administration with postural drainage) are also used in treatment of the established condition. In addition, bronchoscopy for the evacuation of retained secretion has been extensively used in treatment.^{20,22,39,44b,49,59,60,105,127} The results of bronchoscopic aspiration are usually beneficial and relief of symptoms and reëxpansion of the collapsed lung occur with dramatic rapidity. In a few reported cases no bronchial occlusion adequate to explain the collapse present could be seen with the bronchoscope. Bronchoscopy has even been recommended pre-operatively in cases showing excessive bronchial secretion. Excellent results have been reported using endotracheal anesthesia with bronchial suction during operation.^{30c}

The use of pneumothorax for the relief of symptoms due to the displacement of the mediastinum was formerly advocated but does not seem to have been much used in recent years.^{9,40,43,54,72,98}

Breathing air under positive pressure has been shown to reëxpand collapsed lung experimentally⁸² and has also been used clinically.

In so far as a study of the successful methods of prevention and treatment of collapse sheds any light on the etiology of the condition, it supports the idea that collapse is due to bronchial occlusion by retained secretion.

Summary. Massive collapse of lung is most likely to occur under conditions where respiratory movements and bronchial drainage are interfered with and vital capacity is reduced. The constant finding of a decrease in the intrapleural pressure on, and a shift of the mediastinum toward the side of the collapse proves that there must be an active diminution in the thoracic contents on that side. Such a decrease could result only from absorption of air following bronchial occlusion or from expulsion of air by active contraction of lung. The balance of evidence favors the view that the collapse is due to bronchial occlusion. Certain cases of rapid collapse cannot be explained on this basis and may be due to actual contraction of bronchial and pulmonary musculature. An allergic factor may be important in some cases. The bronchial obstruction theory serves as a reliable guide to prevention and treatment.

REFERENCES.

- (1.) Adams, W. E., and Livingstone, H. M.: *Arch. Surg.*, 23, 500, 1931. (2.) Adams, W. E., and Singer, J. J.: *Am. Rev. Tuberc.*, 31, 373, 1935. (3.) Adams, W. E., and Vorwald, A. J.: *J. Thorac. Surg.*, 3, 633, 1933. (4.) Adams, W. E., Hrdina, L., and Dostal, L. E.: *Ibid.*, 4, 377, 1935. (5.) Allen, K. D. A.: *Radiology*, 16, 492, 1931. (6.) Andrus, W. DeW.: *Arch. Surg.*, 10, 506, 1925. (7.) Ball, R. P.: *Ibid.*, 17, 82, 1928. (8.) Band, D., and Hall, T. S.: *Brit. J. Surg.*, 19, 387, 1932. (9.) Beaumont, G. E.: *Brit. Med. J.*, 1, 314, 1935. (10.) Beecher, H. K.: *J. Clin. Invest.*, 12, 651, 1933. (11.) Beecher, H. K., Bradshaw, H. H., and Lindskog, G.: *J. Thorac. Surg.*, 2, 444, 1933. (12.) Bergamini, H., and Shepherd, L. A.: *Ann. Surg.*, 86, 35, 1927. (13.) Bergh, G. S.: *Minnesota Med.*, 16, 105, 1933. (14.) Birnbaum, G. L.: *Ann. Surg.*, 99, 379, 1934. (15.) Bowen, D. R.: *Am. J. Roentgenol.*, 21, 101, 1929. (16.) Boyd, G. L.: *J. Am. Med. Assn.*, 105, 1832, 1935. (17.) Bradford, J. R.: *Quart. J. Med.*, 12, 127, 1918. (18.) Brill, S., Prinzmetal, M., and Brunn, H.: *J. Thorac. Surg.*, 1, 243, 1931. (19.) Briscoe, C.: *Lancet*, 2, 513, 1931. (20.) Brown, A. L.: *J. Am. Med. Assn.*, 95, 100, 1930. (21.) Brown, A. L., and Debenham, M. W.: *Ibid.*, 99, 209, 1932. (22.) Brunn, H., and Brill, S.: *Ann. Surg.*, 92, 801, 1930. (23.) Butler, E. F.: (a) *J. Thorac. Surg.*, 2, 589, 1933; (b) *Ibid.*, 4, 580, 1935. (24.) Butler, E. F., and Fish, H. S.: *Ibid.*, 3, 207, 1933-34. (25.) Carlson, H. A.: *Ibid.*, 2, 196, 1932. (26.) Christopher, F., and Shaffer, J. M.: *Am. J. Surg.*, 32, 197, 1936. (27.) Churchill, E. D.: *Arch. Surg.*, 11, 489, 1925. (28.) Churchill, E. D., and McNeil, D.: *Surg., Gynec. and Obst.*, 44, 483, 1927. (29.) Clarke, J. A., Jr.: *Arch. Int. Med.*, 45, 624, 1930. (30.) Coryllos, P. N.: (a) *Am. J. Med. Sci.*, 178, 8, 1929; (b) *Am. Rev. Tuberc.*, 28, 1, 1933; (c) *J. Thorac. Surg.*, 28, 3, 441, 1934. (31.) Coryllos, P. N., and Birnbaum, G. L.: (a) *Am. J. Roentgenol.*, 22, 401, 1929; (b) *Arch. Surg.*, 19, 1346, 1929; (c) *Ibid.*, 18, 190, 1929; (d) *Ibid.*, 21, 1214, 1930. (32.) Cummings, R. E.: *Arch. Pediat.*, 52, 623, 1935. (33.) Cutler, E. C., and Hunt, A. M.: *Arch. Surg.*, 1, 114, 1920. (34.) Cutler, E. C., and Wood, C. B.: *Surg., Gynec. and Obst.*, 59, 501, 1934. (35.) Dawkins, C. J. M.: *On the Incidence of Anæsthetic Complications and Their Relation to Basal Narcosis*, published for Middlesex Hosp. Press by John Murray, 1936. (36.) Dixon, W. E., and Brodie, T. G.: *J. Physiol.*, 29, 97, 1903. (37.) Drastich, L., Adams, W. E., Hastings, A. B., and Compere, C. L.: *J. Thorac. Surg.*, 3, 341, 1934. (38.) Editorial: *J. Am. Med. Assn.*, 108, 887, 1937. (39.) Eliason, E. L., and McLaughlin, C. W., Jr.: *Surg. Clin. North America*, 14, 1, 1934. (40.) Elliott, T. R., and Dingley, L. A.: *Lancet*, 1, 1305, 1914. (41.) Ellis, M.: *J. Physiol.*, 87, 298, 1936. (42.) Elwyn, H.: (a) *J. Am. Med. Assn.*, 82, 384, 1924; (b) *Ibid.*, 79, 2154, 1922. (43.) Farris, H. A.: *Canad. Med. Assn. J.*, 15, 808, 1925. (44.) Faulkner, W. B., Jr.: (a) *J. Am. Med. Assn.*, 95, 1325, 1930; (b) *Am. J. Surg.*, 12, 27, 1931. (45.) Faulkner, W. B., Jr., and Faulkner, E. C.: (a) *Northwest Med.*, 32, 87, 1933; (b) *Am. J. Med. Sci.*, 184, 370, 1932. (46.) Findlay, L.: *Proc. Roy. Soc. Med.*, 25, 407, 1932. (47.) Flood, R. G.: *Anæsth. and Analg.*, 13, 70, 1934. (48.) Fontaine, R., and Herrmann, L. G.: *Arch. Surg.*, 16, 1153, 1928. (49.) Foreign Letter: (a) *J. Am. Med. Assn.*, 106, 1581, 1936; (b) *Ibid.*, p. 1403. (50.) Foss, H. L., and Kupp, J. H.: *Surg., Gynec. and Obst.*, 51, 798, 1930. (51.) Fuller, C. J.: *Lancet*, 1, 115, 1930. (52.) Gatterdam, E. A.: *Radiology*, 21, 251, 1933. (53.) Gaylor, J. B.: *Brain*, 57, 143, 1934. (54.) Glenn, E. E.: *Am. Rev. Tuberc.*, 23, 507, 1931. (55.) Griffiths, H. F.: *Brit. J. Anæsth.*, 11, 89, 1934. (56.) Gunther, L., and Blond, H. H.: *Am. J. Med. Sci.*, 193, 525, 1937. (57.) Habliston, C. C.: *Ibid.*, 176, 830, 1928. (58.) Hanson, B., and Sjöstrand, T.: *Skandinav. Arch. f. Physiol.*, 71, 123, 1935. (59.) Harrington, S. W.: *Ann. Surg.*, 85, 152, 1927. (60.) Hearn, W. P., and Clerf, L. H.: *Ibid.*, p. 51. (61.) Hoaton, T. G.: *Canad. Med. Assn. J.*, 32, 409, 1935. (62.) Henderson, Y.: (a) *Lancet*, 2, 178, 1935; (b) *Bull. New York Acad. Med.*, 11, 639, 1935; (c) *Diseases of the Respiratory Tract*, Graduate Fortnight, New York Acad. Med., Philadelphia, W. B. Saunders Company, 1936. (63.) Henderson, Y., and Henderson, M. C.: *Arch. Int. Med.*, 49, 88, 1932. (64.) Henderson, Y., Haggard, H. W., Coryllos, P. N., and Birnbaum, G. L.: *Ibid.*, 45, 72, 1930. (65.) Holmes, G. W.: *J. Am. Med. Assn.*, 93, 100, 1929. (66.) Holst, J., Semb, C., and Frimann-Dahl, J.: *Acta chir. Scandinav. (Suppl. 37)*, 76, 1, 1935. (67.) Hudson, W. A., and Jarre, H. A.: *Arch. Surg.*, 19, 1236, 1929. (68.) Hurtado, A., and Fray, W. W.: *J. Clin. Invest.*, 12, 825, 1933. (69.) Jackson, C., and Jackson, C. L.: *Internat. Clin.*, 4, 151, 1932. (70.) Jackson, C., and Lee, W. E.: *Ann. Surg.*

- 82, 364, 1925. (71.) Jacobaeus, H. C.: *Aeta tubere. Scandinav.*, 10, 1, 1936. (72.) Jacobaeus, H. C., and Westermarck, N.: *Aeta radiol.*, 11, 547, 1930. (73.) Jacobaeus, H. G.: *Brit. J. Radiol.*, 3, 50, 1930. (74.) Johnson, J. B., and Crain, C. F.: *Radiology*, 21, 388, 1933. (75.) Kárpáti, G.: *Zentralbl. f. Gynäk.*, 60, 516, 1936 (Ref. *J. Am. Med. Assn.*, 106, 1615, 1936). (76.) King, D. S.: (a) *J. Am. Med. Assn.*, 100, 21, 1933; (b) *Surg., Gynec. and Obst.*, 56, 43, 1933; (c) *Anesth. and Analg.*, 12, 243, 1933. (77.) Knipping, H. W.: *Beitr. z. Klin. d. Tuberk.*, 87, 448, 1936 (Ref. *J. Am. Med. Assn.*, 106, 1525, 1936). (78.) Kountz, W. B., Gottlieb, L., and King, R.: *J. Clin. Invest.*, 15, 601, 1936. (79.) Lambert, A. V. S., and Berry, F. B.: *Ann. Surg.*, 91, 57, 1930. (80.) Lee, W. E., Tucker, G., Ravdin, I. S., and Pendergrass, E. P.: *Arch. Surg.*, 18, 242, 1929. (81.) Lillenthal, H.: (a) *Thoracic Surgery*, Philadelphia, W. B. Saunders Company, 2, 85, 1925; (b) *Arch. Surg.*, 18, 252, 1929 (Discussion of Lee, et al.). (82.) Lindskog, G. E., and Bradshaw, H. H.: (a) *J. Thorac. Surg.*, 3, 333, 1934; (b) *Am. J. Physiol.*, 103, 581, 1934. (83.) Lindskog, G. E., and Van Allen, C. M.: *Arch. Surg.*, 24, 204, 1932. (84.) Lloyd, M. S.: *Am. Rev. Tuberc.*, 23, 476, 1931. (85.) Lubin, M. L.: *Am. J. Surg.*, 19, 80, 1933. (86.) Luisada, A.: (a) *Arch. méd.-Chir. de l'app. respir.*, 5, 320, 1930 (Ref. *J. Thorac. Surg.*, 1, 91, 1931); (b) *Ztschr. f. Biol.*, 95, 434, 1934. (87.) Mackenzie, J. R.: *Brit. Med. J.*, 1, 561, 1932. (88.) Macklin, C. C.: (a) *Physiol. Rev.*, 9, 1, 1929; (b) *Am. Rev. Tuberc.*, 25, 393, 1932; (c) *J. Anat.*, 69, 188, 1935; (d) *Arch. Path.*, 21, 202, 1936; (e) *J. Thorac. Surg.*, 6, 82, 1936; (f) *Med. Rec.*, 143, 89, 1936. (89.) Manges, W. F., and Farrell, J. T., Jr.: *Am. J. Roentgenol.*, 30, 429, 1933. (90.) Mastics, E. A., Spittler, F. A., and McNamee, E. P.: *Arch. Surg.*, 15, 155, 1927. (91.) Matas, R.: *Internat. Clin.*, 2, 1, 1931. (92.) Mathes, M. E., Holman, E., and Reichert, F. L.: *J. Thorac. Surg.*, 1, 339, 1932. (93.) Meese, J.: *Röntgenpraxis*, 8, 173, 1936. (94.) Metcalf, C. R.: *New England J. Med.*, 204, 143, 1931. (95.) Mettenleiter, M. W.: *Am. J. Surg.*, 32, 321, 1936. (96.) Miller, A. K.: *Lancet*, 2, 187, 1936. (97.) Miller, W. S.: *The Lung*, Springfield, Ill., Charles C Thomas, 1937. (98.) Mindline, J.: *Brit. Med. J.*, 2, 1201, 1935. (99.) Moon, V. H.: *Am. J. Path.*, 9, 899, 1933. (100.) Moon, V. H., and Morgan, D. R.: *Arch. Path.*, 21, 565, 1936. (101.) Moore, R. L., Humphreys, G. H., and Cochrane, H. W.: *J. Thorac. Surg.*, 3, 573, 1934. (102.) Morison, J. M. W.: *Brit. Med. J.*, 2, 237, 1930. (103.) Muller, H. J., Overholt, R. H., and Pendergrass, E. P.: *Arch. Surg.*, 19, 1322, 1929. (104.) Myerson, M. C.: *Laryngoscope*, 32, 929, 1922. (105.) Negus, V. E.: *Proc. Roy. Soc. Med.*, 26, 1127, 1933. (106.) Ogawa, C.: *Am. J. Anat.*, 27, 333, 1920. (107.) Overholt, R. H.: *Arch. Surg.*, 21, 1282, 1930. (108.) Overholt, R. H., and Veal, J. R.: *New England J. Med.*, 208, 242, 1933. (109.) Pasteur, W.: (a) *Lancet*, 2, 1351, 1908; (b) *Ibid.*, 2, 1080, 1910; (c) *Ibid.*, 1, 1329, 1911; (d) *Brit. J. Surg.*, 1, 587, 1914. (110.) Patey, D. H.: *Ibid.*, 17, 487, 1930. (111.) Pinchin, A. J. S., and Morlock, H. V.: *Brit. Med. J.*, 1, 930, 1931. (112.) Pottenger, F. M.: *J. Thorac. Surg.*, 1, 75, 1931. (113.) Powers, J. H.: *Ibid.*, 5, 306, 1936. (114.) Prinzmetal, M., and Kountz, W. B.: *Medicine*, 14, 457, 1935. (115.) Prinzmetal, M., Brill, S., and Leake, C. D.: *Surg., Gynec. and Obst.*, 56, 129, 1933. (116.) Reinberg, H., Kopziorskaja, L. Z., and Zatkin, S.: *Deutsch. Ztschr. f. Chir.*, 230, 182, 1931 (Ref. *J. Thorac. Surg.*, 1, 93, 1931). (117.) Reinhardt, E.: *Vireh. Arch. f. path. Anat.*, 292, 322, 1934. (118.) Richards, G. E.: *Am. J. Roentgenol.*, 30, 289, 1933. (119.) Rovenstine, E. A., and Taylor, Q. B.: *Am. J. Med. Sci.*, 191, 807, 1936. (120.) Ryan, T. J.: *J. Am. Med. Assn.*, 107, 267, 1936. (121.) Sante, L. R.: *Ibid.*, 88, 1539, 1927. (122.) Scott, W. J. M.: (a) *Arch. Surg.*, 10, 73, 1925; (b) *J. Am. Med. Assn.*, 93, 101, 1929. (123.) Scott, W. J. M., and Cutler, E. C.: *Ibid.*, 90, 1759, 1928. (124.) Scrimger, F. A. C.: *Surg., Gynec. and Obst.*, 32, 486, 1921. (125.) Sheret, J. E.: *Proc. Roy. Soc. Med.*, 23, 487, 1929-30. (126.) Sise, L. F.: *Anesth. and Analg.*, 11, 23, 1932. (127.) Sneller, C. D.: *Illinois Med J.*, 69, 158, 1936. (128.) Snyder, H. E.: *Ann. Surg.*, 102, 5, 1935. (129.) Stivelman, B. P.: *Am. Rev. Tuberc.*, 30, 60, 1934. (130.) Sutcliffe, W. D., and Steele, B. F.: *Arch. Surg.*, 30, 14, 1935. (131.) Van Allen, C. M., and Jung, T. S.: *J. Thorac. Surg.*, 1, 3, 1931. (132.) Van Allen, C. M., La Field, W. A., and Ross, P. S.: *Radiology*, 22, 27, 1934. (133.) Wagoner, G. W.: *Am. J. Med. Sci.*, 171, 697, 1926. (134.) Warner, W. P.: *Quart. J. Med.*, 3, 401, 1934. (135.) Warner, W. P., and Graham, D.: *Arch. Int. Med.*, 52, 888, 1933. (136.) Watter, L.: *Anesth. and Analg.*, 15, 22, 1936. (137.) Wilmer, H. B., Cobe, H. M., and Lee, W. E.: *Ann. Surg.*, 91, 651, 1930. (138.) Wilson, H. B.: *Am. J. Obst. and Gynec.*, 31, 667, 1936. (139.) Woodman, M.: *Proc. Roy. Soc. Med.*, 27, 1517, 1934.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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TRICHINOSIS: AN UNSOLVED PROBLEM IN THE UNITED STATES.

In a series of articles recently appearing in the Public Health Reports of the United States Public Health Service it has been stated that this country has the greatest problem in trichinosis of any country in the civilized world and that the efforts to control this infection during the past two or three decades have brought about little if any reduction.

Frequency of Infestation in Man. Satisfactory estimates of the frequency of the infection of man with trichinæ can only be obtained by the examination of bits of muscle tissue removed postmortem. Hall and Collins¹ have recently completed observations on specimens from 300 diaphragms removed at autopsy from patients dying in 10 hospitals located in Washington, D. C., and one in Baltimore, Md. Since 5 of these hospitals cared for Federal beneficiaries sent from all over the United States and since the population of Washington, D. C., is to an unusual degree drawn from various parts of the country, they believe the sample, though small, to be fairly representative.

The diaphragms were examined for trichinæ by the direct microscopic method and by the digestion-Baerman method. The supplementary value of the second procedure was demonstrated by adding half as many positives again as would have been revealed had direct examination alone been used. In all, 41 of the 300 diaphragms were found to be infected with trichinæ, a frequency of 13.67%.

Including their own observations with those of previous writers who had made similar studies in different parts of the United States there are available in the literature 1778 observations made upon postmortem material. Trichinæ were found in 222 (12.5%). Hall and Collins point out that this percentage cannot be taken on its face value as an average or as an index, on account of the limitations of the methods of examination, the relatively small numbers, and the limited geographic area represented. They are inclined to believe that the percentage is too low rather than too high.

Magath,⁷ on the other hand, has pointed out that only 5 of these studies were made during the last 35 years, and that the material was obtained very largely from bodies examined at necropsy in charity hospitals or from cadavers on dissecting tables in medical schools. It represented, therefore, to a considerable degree those who are down and out, who live from hand to mouth and of necessity eat inferior and poorly prepared food of all sorts.

Magath himself, however, brought further confirmation to the estimate of Hall and Collins. He examined muscles from the bodies of 220 patients who had died of various causes at the Mayo Clinic. This

clinic draws its patients widely from the United States and very largely from the upper income brackets. Two grams of muscle from the diaphragm, the intercostals, the rectus abdominis and the sternocleidomastoid were compressed and searched with a binocular microscope. Trichinae were found in 17 bodies (8%). Magath thought that it was safe to assume that the actual incidence of infection in this series would have been 12 to 15%, had the direct examination been supplemented by a digestion method or 50 to 100 gm. of muscle examined.

Admitting the desirability of more extensive observations over a wider geographic area, the data at present available in the United States indicate that trichinae are found in the muscle tissue of approximately 1 out of every 8 persons at the time of death.

Frequency of Clinical Trichinosis. Of the 41 positive cases found by Hall and Collins none had any previous history of clinically recognized trichinosis, so far as could be ascertained from routine clinical histories taken during their last hospital admission. Yet in one of the cases there were between 900 and 1000 trichinae per gram of diaphragm muscle. In the 17 cases discovered by Magath at the Mayo Clinic, with exceptionally complete and accurate records, only 7 gave a history of symptoms suggestive of infection, but these were readily explained on the basis of other conditions found. In not a single instance in either series had the diagnosis of trichinosis been established before death.

The occurrence and severity of symptoms are largely determined by the number of trichinae, their organ distribution, the rapidity of the invasion and the resistance, natural or acquired, offered by the tissues of the host. So far as numbers are concerned, Hall and Collins⁴ think that it is safe to say that in infestations with over 100 larvae per gram there must be pronounced clinical symptoms. In infestations with less than 1 larvae per gram symptoms are either absent or negligible. Sufficient data are not yet available to permit more accurate statement of the clinical threshold. Enough evidence is available however, to state that the vast majority of individuals who acquire infestations with this parasite are unaware of its presence in the body and suffer no appreciable handicap therefrom. In a small proportion which the figures of Hall and Collins would suggest to be about 1 in 20, the distribution and intensity of the infestation is of sufficient degree to cause considerable damage to the host and to produce symptoms which are sufficiently characteristic to permit clinical recognition.

Ransom⁹ found that among the 1550 cases reported in the United States from 1842 to 1915, there were 240 deaths, a case fatality rate of about 16%. Since the reported cases would tend to be weighted to an unusual degree by severe infections, this rate is only an approximation and probably higher than would be found if all clinically recognizable infections were included. It can only be used with this reservation.

Implications of the Data. By applying the ratios obtained in these studies to the population of the United States, Hall and Collins conclude that "the problem (of trichinosis) is one of major importance, apparently affecting, to some degree, as a conservative estimate, several million persons, with clinical trichinosis in some form affecting possibly several hundred thousand persons, and with possibly several thousand deaths."

Even granting that the rates obtained from these very small samples are representative of the whole population of the United States, one

might question whether these statistical inferences are permissible. The frequency of infestation was based upon persons who had died, and not upon persons who were living. The encysted trichinæ which were found, in many instances dead and calcified, had been introduced into the tissues some months or years previously, or represented the cumulation of repeated doses over a long period of years. One cannot infer, therefore, that the frequency of finding trichinæ postmortem is synonymous with the incidence of the infection in the living.

Again, the age distribution of persons who have died is not the same as the population who are living, and Hall's^{3a} data indicate that the frequency of infestation varies with age, being lowest during the first two decades of life.

By analogy, even though 50% of persons show evidence at post-mortem of a healed focus of tuberculous infection, to infer from this that 50% of the population are suffering from tuberculosis is obviously misleading. It can only be inferred that at least 50% at the time of death have been infected with tuberculosis sometime during life.

With these considerations in mind, it would seem to be more nearly in accord with the ascertained facts to state that as high a percentage as 12.5% of the 1,400,000 persons who die each year in the United States (175,000 persons) may show evidence of having acquired an infestation with trichinæ at some time previous to death, and that, in perhaps 1 out of 20 of these (8750) the infestation was sufficiently severe to cause symptoms. Assuming in the latter group the case fatality rate to be as high as 16% (Ransom), 1400 of these deaths might have been caused by this parasite, as a liberal estimate.

Stated on this basis there is still reason for agreeing with Hall and Collins that exposure to infestation with trichinæ is far more frequent than is commonly realized, that morbidity and mortality reports fail to indicate the real extent of the problem, that a considerable proportion of infestations which are clinically recognizable, and even of deaths due to this cause, escape recognition.

Clinical Recognition. In a paper on "The Complex Clinical Picture of Trichinosis, and the Diagnosis of the Disease," Hall^{3b} maintains that the most serious gap in our knowledge of trichinosis, so far as medical practice is concerned, is our ignorance of the clinical picture. The question might be raised whether it is so much a matter of ignorance of the clinical picture, which has been very fully described by numerous medical writers during the past 50 years, as it is a matter of failure to suspect such a cause of illness because of its (supposed) rarity, and because the symptoms presented in a large proportion of cases are so irregular and protean in character as to render differentiation from other disease conditions difficult or impossible without the aid of a specific diagnostic test.

When a group of individuals are infected at the same time, as in the family reported by Otto and Janney,⁸ and the epidemic reported by Drake, Hawkes and Warren,¹ sooner or later the diagnosis will probably be suspected, particularly if the affected group are of foreign extraction and if a definite history of having eaten raw, partially cooked or insufficiently processed pork products can be obtained. Even when the epidemiologic evidence of the nature of the illness is strong, it is not easy to establish the clinical diagnosis with certainty, and when cases occur singly or sporadically this difficulty is augmented.

The value and limitations of laboratory aids—particularly the differential blood count (eosinophilia), the biopsy, the skin test and the precipitin test—have recently been discussed by Friedlander,² Spink and Augustine,¹⁰ Heathman,⁵ Kaljus,⁶ Magath,⁷ and Hall.^{3b} When negative, they are of no value. When positive, the difficulty is in distinguishing between a reaction due to acute trichinosis, *i. e.*, the stage of invasion—and one due to an invasion which took place months or years before and has since become latent and healed.

After reviewing these discussions, one can only agree with Hall^{3b} that more accurate and specific tests for the diagnosis of acute trichinosis are highly desirable, but, after diagnosis, what? Possibly in the future some usefully chemotherapeutic measure will be developed. On the basis of present knowledge the problem is one of prevention.

Control. To dismiss the problem of prevention by stating that there is still need for emphasizing the importance of cooking pork thoroughly before it is consumed, is somewhat analogous to an attempt to control milk-borne disease by advising the general public not to drink raw or improperly pasteurized milk. Moses recognized the human limitations to such advice some two thousand years ago, and forbade the eating of pork.

Aside from this gratuitous advice, the present control program is limited mostly to Federal supervision of the refrigeration and processing of those pork products customarily eaten without cooking. "Unfortunately, almost one-third of our meat supply comes from houses not shipping in interstate commerce and therefore not under Federal inspection or an equivalent inspection; and as sold or as served in public eating places, uninspected pork products are shuffled, indistinguishably, with inspected products, some places selling or serving inspected, and others uninspected products."^{3c} Moreover, as Hall would be the first to admit, the inspection of hogs, even as carried out under the direction of the Federal Bureau of Animal Industry, does not, and has not for many years, attempted, nor claimed that it could, eliminate trichinous pork. It has only decreased the exposure and dosage, by improving methods of processing, *i. e.*, refrigeration, smoking, curing, and so forth, of pork products.

The prevention of human trichinosis rests in the last analysis upon control of the disease in swine. Hall^{3c} estimates that the incidence of live trichinae in swine over the country as a whole is between 1 and 2%. This incidence will vary, apparently from 0% in swine raised under the swine-sanitation system, through a small fraction of 1% in Southern swine and 1.5% in grain fed swine, to between 4 and 5% in garbage-fed hogs. Furthermore, he states that the status of trichinosis in these groups of swine has not changed materially in the past 50 years.

He believes that the parasitic cycle of trichinosis in hogs is maintained by swine eating pork scraps in garbage containing encysted larvae, supplemented to a small and insignificant degree by swine eating the remains of infected rats. Hence, he reasons that to the extent that pork scraps are excluded from garbage, or better, to the extent that garbage-feeding is discontinued, trichinosis will decrease and disappear. Moreover, he states that there are reasons for believing that garbage feeding is economically unsound. If his premises are correct, then there is no insuperable obstacle in the way of control. In fact, one

might ask why the Federal Bureau of Animal Industry, the packing industry, and the swine-raising industry have not made progress in this direction during the past 40 years. The preventive problem is veterinary rather than medical, and from the human point of view an important one.

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REFERENCES.

- (1.) Drake, E. G., Hawkes, R. S., and Warren, M.: J. Am. Med. Assn., 105, 1340, 1935. (2.) Friedlander, R. D.: AM. J. MED. SCI., 188, 121, 1934. (3.) Hall, M. C.: (a) Pub. Health Repts., U. S. P. H. S., 52, 512, 1937; (b) Ibid., p. 539; (c) Ibid., p. 873. (4.) Hall, M. C., and Collins, B. J.: Ibid., p. 468. (5.) Heathman, L. S.: Am. J. Hyg., 23, 397, 1936. (6.) Kaljus, W. A.: Puerto Rico J. Pub. Health and Trop. Med., 11, 768, 1936. (7.) Magath, T. B.: J. Am. Med. Assn., 108, 1964, 1937. (8.) Otto, G. F., and Janney, J. H., Jr.: Am. J. Hyg., 25, 76, 1937. (9.) Ransom, B. H.: Rept. 18th Ann. Meet. U. S. Live Stock San. Assn., pp. 1-19, 1915. (10.) Spink, W. W., and Augustine, D. L.: J. Am. Med. Assn., 104, 1801, 1935.

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ORIGINAL ARTICLES.

WHAT IS LIPEMIC NEPHROSIS?*

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IN this paper I shall discuss what is known as chronic genuine nephrosis or chronic lipemic nephrosis, wholly omitting such subjects as amyloid nephrosis, necrotizing nephrosis, febrile albuminuria, sublimate nephrosis, and so forth. It is chronic lipemic nephrosis, and not the other types, which has caused a great deal of discussion and research in the past 20 years and which has caused every internist a great deal of intellectual difficulty.

In 1914 Vollhard and Fahr,¹² in their monograph on Bright's disease, set apart for the first time the entity which they called "chronic genuine nephrosis." They sharply defined, both clinically and anatomically, this supposedly distinct nephropathy. Since that time, many papers have been written about chronic genuine nephrosis, or as it is now more commonly known in the United States, chronic lipemic nephrosis. In my opinion, the general practitioner has been caused an unnecessary amount of difficulty because of this new name and also because of the introduction of certain conceptions that had previously not been considered in discussing kidney disease. I shall try to clear up this subject in a very simple way. At the outset, I want to state that pure forms of chronic nephrosis are really very rare. I have been looking for this condition since 1916 and have seen only 10 cases among the large number of nephropathies seen by me during this period. Vollhard, who has probably

* Lecture delivered at Oklahoma City Clinical Association, 1933, and before the Lackawanna County Medical Society, 1935.

the largest material in kidney disease in the world at his command, speaks of its rarity. The pediatricians apparently see relatively more of this disease than do the internists. On the other hand, many of the cases described as chronic lipemic or chronic genuine nephrosis are, in fact, not chronic genuine nephrosis in the strict sense of the term, but are actually cases of glomerulonephritis which have in addition to the symptoms and laboratory findings characteristic of glomerulonephritis many of the characteristics of a lipoid nephrosis, the so-called subacute or subchronic glomerulonephritis with "*nephrotischem Einsehlag*."

At this point it may well be asked, what, then, is chronic lipemic nephrosis in the strict sense of the term? From the standpoint of symptomatology, it is a condition in which a most severe hydrops develops, as a rule insidiously. There is often a tremendous anasarca which, when a trocar is inserted into the lower extremity, results in the draining off of quarts of edema fluid, containing the water and salts of the blood plasma but none or extremely little of the albumin of the plasma. In other words, this edema fluid is a nearly pure transudate or ultrafiltrate.* There is usually a marked ascites and usually also hydrothorax on one or both sides. At autopsy, in cutting through the muscle and the connective tissue, one can sometimes see edema fluid oozing out from the interstices of the connective tissue. In addition, the patient usually has an anorexia which may be extremely severe, so that there is a marked reduction in the intake of food. In my estimation, some of these patients actually die of inanition. The patients are pale and weak, though not a few can carry on in their work or profession for some time, especially if most of the edema is removed by therapeutic measures. The most common cause of death is usually stated to be a pneumococcus peritonitis. Other causes of death are streptococcus peritonitis, pneumonia, and inanition. One of my 10 cases of pure nephrosis died in uremia. This important case will be described later in this paper.

I want to emphasize that according to the strict definition of true chronic nephrosis, the blood pressure is always normal and must be normal. A little farther on in this paper I am going to discuss 2 of my cases which were seemingly exceptions to this rule. One was an undoubted pure case, substantiated by the very careful autopsy studies of Dr. E. T. Bell, Professor of Pathology at the University of Minnesota. The other, on careful microscopic examination, showed minimal endothelial cell proliferation in some of the glomeruli, so that it was not 100% pure. In both cases high blood pressure developed before death. The study of these two kidneys by Dr. Bell together with the experimental studies of Bell,³ Goldblatt,⁵ Collins,⁴ and Page¹¹ has thrown a most interesting light upon the mechanism of hypertension in kidney disease, and demonstrates

* This fluid contains from 0 to 0.15% of protein, averaging about 0.1%.

why the blood pressure is ordinarily not elevated in pure nephrosis. These cases will be described later in this paper.

The patient with chronic nephrosis has a severe obliguria, passing from 200 to 600 cc. of fluid during the 24-hour period. A specific gravity of from 1.025 to 1.050 is nearly always found, unless a diuresis has been induced by some method. There is a heavy flocculation of albumin, usually termed 4+, there being from 1 to 5% of albumin content in the urine and the daily output ranging from 10 to 30 grams or even more in a day. There are hyaline and granular casts in abundance. Sometimes the casts are studded with little highly refractile globules which, under the Nicol prisms, are seen to be doubly refractile. These small highly refractile globules may also be seen floating in the urine. They are cholesterol droplets. In a true case of genuine nephrosis, there are no red blood cells in the urine.* There are, on the other hand, always a few white cells. The urine occasionally shows traces of sugar and even moderate quantities of sugar at times, especially after a diet containing considerable carbohydrate. It has been found that this is a true renal glycosuria probably due to the fact that the reabsorption of sugar from the glomerular filtrate in the anatomically altered convoluted tubules of the kidney is impaired. If gum acacia or Congo red are introduced intravenously, then these substances appear in large quantities in the urine very soon. These two colloids are not found in the urine from normal kidneys. The Congo red and gum acacia particles leak through the glomerular ultrafilter and appear in the urine exactly in the same manner as the serum albumin particles of the plasma do.

Physicians of the older generation will say I am describing what they were brought up to call chronic parenchymatous nephritis or chronic tubular nephritis. Let me state at once that they are right, because what was formerly called chronic parenchymatous nephritis or chronic tubular nephritis is today divided into chronic genuine or lipemic nephrosis and subchronic glomerulonephritis with a nephrotic tendency (nephrotischem Einschlag) by those who follow the Volhard and Fahr classification.

What does the blood show? It shows that the serum albumin is reduced to extremely low values, around 1 to 3% instead of the normal 4 or 5%. The globulin remains at the normal value or seems even to increase at times. Fibrinogen seems always to be somewhat increased. Because of the lowered serum albumin content of the blood, the so-called colloid osmotic pressure is reduced to one-half or even less.

There is an increased neutral fat content of the blood and the values for cholesterol are doubled or tripled. On viewing the serum,

* One or two red blood cells per medium power field are occasionally seen in the urine of normal persons if a careful search is made. Not more than this many are seen in nephrosis.

one frequently notes that it is milky or creamy because of the large number of lipoid particles it contains. Hence the name lipemic nephrosis. There is usually some slight anemia or even a moderate anemia. Our experience has shown that careful determinations of the blood plasma volume usually show it to be somewhat, or even considerably, reduced. In other words, just the opposite of a plethora or hydremia is present. There is no increase in the metabolites of the blood, such as the non-protein nitrogen, the urea, the creatinine, the indican, and so forth.

Let us now inquire as to the kidney function. The water output is remarkably reduced and with this, the output of salt. But, as I will show a little later, this is not due to a diminution in kidney function, but is a result of the loss of serum albumin and the consequent reduction in the colloid osmotic pressure. In consequence of the lowered colloid osmotic pressure, water and salt filter off from the plasma in the capillaries to form edema. The urine output is reduced exactly by the amount of water and salt retained as edema. In my experience, the output of phenolsulphonephthalein dye is normal, or even increased when the test has been made by intravenous injection of the dye and when the urine has been obtained by catheterization and irrigation of the bladder to obtain all the urine in the bladder. The concentration test is normal. There is no tendency whatsoever to true uremia, nor to pseudouremia or eclamptic uremia. At times, there seems to be a slight haziness about the nerve head which suggests the possibility of some edema; otherwise the eyegrounds are normal.

The basal metabolism is nearly always lowered to values of from -10 to -30%, which has suggested to certain physicians that nephrosis may be a disease of metabolism. In only one case have I ever found outright symptoms of myxedema in nephrosis, and in this case the nephrosis cleared up with the cure of the myxedema by thyroid extract. When the thyroid extract was no longer taken, both the symptoms of myxedema and of nephrosis reappeared in the patient.

PATHOLOGY. The kidney at autopsy is seen to be slightly or much enlarged, to be pale grayish-yellow, and to look fatty. On microscopic examination, the convoluted tubules show swelling of the cells and infiltration with hyaline droplets or infiltration with fat and lipoid bodies which are doubly refractile. Using the ordinary hematoxylin-eosin stain, only slight changes or none at all are seen in the glomeruli. The earliest accounts of histologic examination stated that the glomeruli were altogether normal. On the other hand, Dr. E. T. Bell,² of the department of pathology at the University of Minnesota, using the azocarmine dye, has shown that the glomerular basement membrane shows distinct changes in many cases. These are a thickening of this membrane and apparently some fraying out of the membrane. In other words, the filtering

membrane in many cases of this disease seems to have undergone some anatomic change. It can no longer be said that the glomeruli are normal, because as this disease progresses, this basement membrane gets thicker and thicker, at times to such a degree that the circulation in the glomerular loops may be throttled. In consequence, high blood pressure may develop and renal insufficiency and uremia may result from the impaired flow of blood through the glomerulus and the marked decrease in the area of filtering surface brought about by this thickening of the basement membrane. This happened in two of our most interesting cases, on which we have complete autopsy examinations. In my opinion, this thickening of the basement membrane, but more especially the changes in its function as an ultrafilter, are the crux of the whole situation in chronic lipemic or chronic genuine nephrosis.

As to the etiology of the disease, frequently it is altogether unknown. I have seen one case develop after a sore throat, much as acute glomerulonephritis does, but without the hypertension, hematuria and renal insufficiency characteristic of true glomerulonephritis. I have seen one case in a physician, apparently after a severe streptococcus infection of the finger. The finger finally healed, but during the infection, what was called nephritis developed. When I saw the patient about 2 years after the original infection, he had a typical case of true chronic lipemic nephrosis. In children it is often associated with a purulent sinusitis from which *Staph. albus* can be cultured. I have seen one case associated with a true myxedema which cleared up completely after curing the myxedema on thyroid administration. Occasionally syphilis will cause a chronic nephrosis. Many of the cases develop insidiously without any clear-cut evidence for an etiologic agent.

Now that I have given you this picture of chronic lipid nephrosis, let us see what he can make out of it through our knowledge of modern physiology and research. To my mind, all the symptoms of the disease can be easily explained on the well-founded assumption that the ultrafilter of the glomerulus, which has been shown in most cases to be altered morphologically by the newer staining methods, has become permeable to serum albumin and other colloids of small size. Therefore the serum albumin in the blood filters off into the urine day by day. The content of serum albumin in the blood is hereby reduced to such values that the colloid osmotic pressure of the blood is lowered to about one-half.

At this point let me say just a word or two about this osmotic pressure of the colloids of the blood. In my estimation, the only known function of the serum albumin in the blood plasma is to produce a colloid osmotic pressure within the capillaries of the body. Because the serum albumin can not pass through the capillary wall as the salts and water can, the colloid osmotic pressure is effective only inside the capillaries and therefore tends to hold water within

the capillaries against the hydrostatic pressure in these capillaries which tends to filter off the water and salts of the plasma into the tissue as an ultrafiltrate. If we had not this colloid osmotic pressure, all the water and salts of our blood would, within a very few hours, leave the blood-vessels as a transudate and our blood would dry up to corpuscles.

Figure 1 is a diagram which illustrated what happens in the normal capillaries of the body when blood of normal colloid osmotic pressure flows through them. For the hydrostatic pressures at the arterial

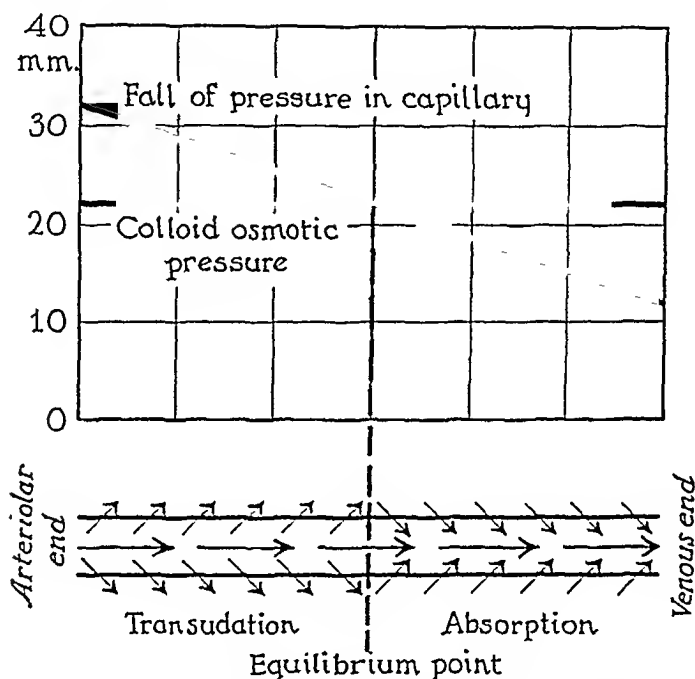


FIG. 1a.—Diagram of normal fall in pressure along human capillaries from the arterial end to the venous end, together with a normal colloid osmotic pressure. Plasma fluid is filtered out from the arterial half of the tube and reabsorbed in the venous half.

and venous ends of the capillaries I have used the averages obtained by Landis⁹ from direct measurements on the capillaries of normal men. The normal colloid osmotic pressure I have taken as being 22 mm. Hg.⁶ At the arterial half of the capillary there is ultrafiltration of water and salts from the capillaries into the surrounding tissue space, because the blood pressure or hydrostatic pressure is greater than the colloid osmotic pressure of the plasma proteins, and in consequence fluid and salts must pass out of the capillary as an ultrafiltrate or transudate. From the middle of the capillary on to the venous end the capillary blood pressure is less than 22 mm. Hg, and therefore water and salt must reënter the capillary, be-

cause the colloid osmotic pressure is higher than the hydrostatic pressure. The net result is: no loss of fluid from the blood plasma with normal colloid osmotic pressure flowing through this normal capillary. In Figure 2 is shown what must happen in a capillary if the blood pressure remains normal, but if the colloid osmotic pressure of the plasma is reduced to 12 mm. Hg. In this latter case the blood pressure is higher than the colloid osmotic pressure from the arterial to the venous end and filtration of water and salts will take place all along the capillary and there will be no reabsorption

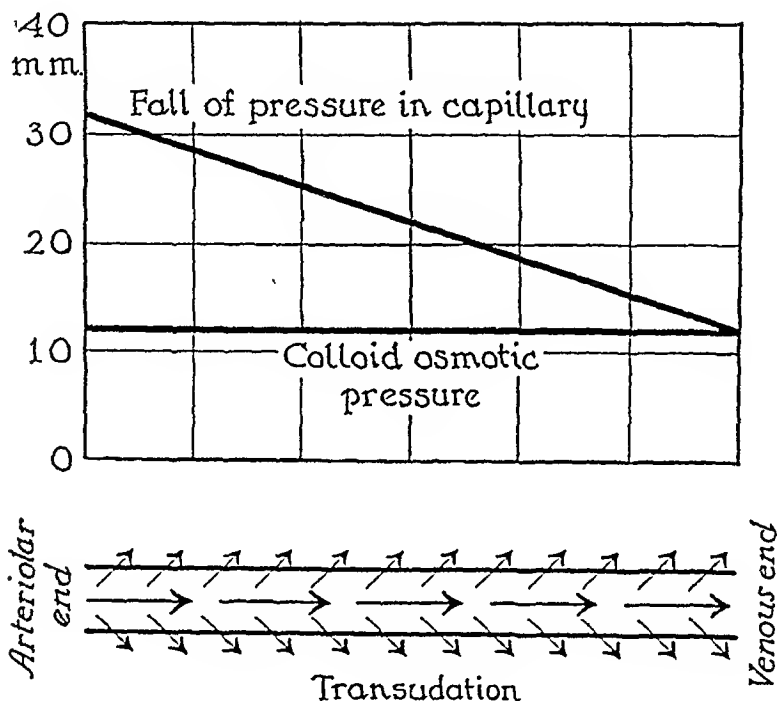


FIG. 1b.—Diagram of normal fall in pressure along the capillary, with low colloid osmotic pressure of 12 mm. Hg. Plasma fluids must be filtered out along the whole course of the capillary from arterial end to venous end, and this fluid, collecting in the interstices of the white fibrous connective tissue, becomes edema.

in this capillary. The excess fluid may be partly taken care of by the flow of lymph away from the area, but some fluid will remain as edema and less fluid will get to the kidneys for filtration. The result will be edema and oliguria, both due to reduction in colloid osmotic pressure alone.

Therefore when the colloid osmotic pressure in nephrosis is reduced to one-half or near it, much of the ingested water and salt is filtered off into the skin and other tissues. Under these circumstances only a small portion of the ingested water and salt is available for filtration in the glomeruli of the kidneys and the urine output is reduced to a small fraction of the ingested water and salt. The water and salt filtered off in the capillaries accumulates in the

subcutaneous and other connective tissue reservoirs and we begin to have an edema. This has been proved by research work done on animals by Leiter,¹⁰ Barker,¹ Fahr and Kerkhof.⁵ If we take away from our experimental animals by plasmapheresis* so much of the serum albumin and globulin that the colloid osmotic pressure is reduced to one-half, then our animals develop the same kind of hydrops as do our patients with chronic nephrosis. A diuresis follows at once and a rapid removal of the edema fluid takes place if gum acacia, an indifferent colloid, is injected into the veins of our patients or into the veins of our experimental dogs suffering from this type of edema. The gum acacia serves only to raise the colloid osmotic pressure of the blood plasma. Edema fluid in large quantities is then drawn into the capillaries and circulates with the blood plasma to the kidneys where it is rapidly removed as urine. Not infrequently one can see the distended veins swollen with the increased blood volume due to the absorption of the edema fluid. Blood volume determinations done after the injection of the gum acacia prove that the blood plasma volume is increased and that actually a plethora or hydremia has been produced.

The experimentally produced hydrops has been proved by our researches to be a true transudate, containing very little of the protein of the blood, but containing salts and water. The edema fluid in our experimental animals is the same as in nephrosis. Moreover, in these animals when we begin to remove the serum albumin of the blood and to lower its protein content, the lipid and fat content of the blood immediately rise somewhat. And just as the plasma volume is reduced in chronic lipemic nephrosis, so also is the plasma volume reduced in our dogs in these experiments, despite the fact that there has been no loss of corpuscles. When gum acacia is injected, the plasma volume increases to the normal or higher values.

Very much has been made of the low basal metabolic rate by many authors in discussing the etiology of the condition. In my estimation, there are three factors producing this low basal rate. First, in calculating the basal metabolism from the height-weight formula, we usually do not subtract the weight of the accumulated water. The inclusion of this extra weight of water in the calculation tends to lower the determined basal metabolism as over against the calculated one by about 5 to 10%. Also I have determined on some of my cases that these patients eat much less than their basal requirements and therefore are in a state of chronic starvation. As is well known, chronic starvation reduces the basal metabolism.

* By plasmapheresis we mean the abstraction of serum protein from the blood plasma. The dogs are repeatedly bled from the right heart or jugular veins. The blood plasma is pipetted off the centrifugalized blood corpuscles. The blood corpuscles plus Ringer's solution is reinjected. If done carefully there is no reduction in the number of red cells in the blood but a very marked reduction in the plasma proteins. We have produced a severe edema within 24 hours in our dogs by this method.

A diet of 800 calories per day sometimes lowers the basal metabolic rate as much as 10%. I have had one patient with a subchronic glomerulonephritis with a strong nephrotic tendency who lived on an intake of about 500 calories per day for some months and finally died of inanition. His basal rate was around -20%. Moreover, I am inclined to believe that the thyroid hormone circulating in the blood may be filtered off to a considerable amount in the urine just as are serum albumin, gum acacia, Congo red, and other colloid particles of small size. I have given enormous quantities of thyroid extract, 10 to 15 grains, daily to these patients without raising the basal metabolism more than a few degrees and without causing symptoms of hyperthyroidism. These same quantities given to normal persons or even to patients with true myxedema would probably raise the basal rate far above the normal and would cause symptoms of tachycardia, nervousness, palpitation and weakness. In fact, I have seen what was apparently exophthalmos develop in 2 patients with myxedema who were given doses of thyroid extract comparable to doses that are frequently given in the treatment of chronic nephrosis without the production of symptoms of hyperthyroidism.

There may very well be a moderate degree of hypothyroidism present in chronic nephrosis, but of a degree insufficient to produce outspoken symptoms of myxedema. Barker¹ has shown on animals that a chronic lowering of serum protein by plasmapheresis leads to a lowered basal rate. It is possible that Barker's dogs did not eat as well as normal dogs and in removing the serum proteins by plasmapheresis circulating thyroid hormone was removed at the same time, both tending to lower the basal rate. The above mentioned factors, I think, will explain the lowered basal rate in most cases. Certainly very few of the cases have the mental characteristics of myxedema in any severe degree, and there does not seem to be either the skin change, the loss of hair, or the intolerance to cold so characteristic of myxedema.

It is a well known fact that hypercholesteremia follows hypothyroidism and lowered basal rate. I believe that some of the hypercholesteremia of chronic nephrosis is associated with the hypothyroidism and lowered basal rate. There is also experimental evidence found in plasmapheresis experiments that an increased cholesterol and neutral fat content of the blood plasma follows depletion of the proteins of the blood plasma.² In some of our own experiments on plasma protein depletion in dogs, we saw increases in the plasma lipoids appear. Therefore it does not seem necessary to call in other mechanisms to explain the lipemia of chronic nephrosis.

In our dogs we find exactly what we find in these patients, except that we remove the serum albumin from the blood mechanically, whereas in chronic nephrosis it is removed by a pathologic permeability of the glomerular membrane which is normally impermeable

to serum albumin and globulin. I think it can be said that, although we have not produced the characteristic picture in the kidney of chronic genuine nephrosis, we have produced in our animals the symptomatology of chronic lipemic nephrosis and have learned something of the exact mechanism of the production of these symptoms. The pathologic changes in the kidney of nephrosis, our knowledge of kidney function, and the data obtained from our dogs in which the plasma proteins have been depleted compel us to believe that chronic genuine or lipemic nephrosis is a disease of the glomerulus of the kidney, of such a nature that where as previ-



FIG. 2a.—Photomicrograph of a glomerulus in a case of pure nephrosis which died in uremia. The basement membrane thickening and the intense narrowing of the lumen of many of the glomerular capillaries can be seen. Many glomeruli are completely closed and hyalinized. Azo carmine stain.

ously it held back serum albumin and allowed the plasma to be filtered off as an ultrafiltrate, now in this disease, it has become permeable also to serum albumin and as the plasma water and salt filters off in the glomerulus, part of the serum albumin goes with it and is found in the urine. The reduction of the content of the serum albumin in the blood lowers the colloid osmotic pressure and this leads to an increased formation of transudate in all the capillary areas of the body. This transudate forms faster than the lymph flow can remove it and edema develops.

Moreover, our experiments on animals and on patients have proved that the retention of salt is due to the lowering of the colloid

osmotic pressure and the accumulation of edema, rather than that the salt causes the edema in itself. In our animals we have lowered the serum albumin content to one-half or less and then we have replaced a large part of the serum protein of the blood by gum acacia, keeping the colloid osmotic pressure nearly normal by means of the gum acacia. Under these circumstances, water output was normal, no edema formed and no salt retained. We have replaced the serum albumin in our patients by another colloid, gum acacia, and have caused the absorption of the edema in this disease and have produced a very good diuresis of water and sometimes as much as a tenfold increase in the daily output of salt. Moreover, in our animals the neutral fat increase in the blood is shown to be partly due to the reduction of the serum protein content in the blood.

The degenerative changes in the convoluted tubules are as yet not well explained. For myself, I believe that the infiltration with fat and lipid is due to the fact that there is an increased content of the fat and lipid in the blood and in consequence the glomerular filtrate which passes down the kidney tubules probably has a high fat and cholesterol content. We know there is always some fat and lipid in the urine. It is not at all improbable from our knowledge of kidney function that the cells of the tubules simply infiltrate with this lipid and fat and possibly also with albumin. We have not yet gone far enough in our experiments to prove this point, but Barker¹ has described hyaline droplets and fatty infiltration in the kidneys of his dogs with reduced plasma protein content and high lipid content of the plasma.

Certainly from the present state of our knowledge of the physiology of these kidneys, there is no marked change in the function of the tubules, excepting occasionally some sugar in the urine, which is the only indication that I have ever found that the tubular function is damaged in this disease. It is now well known that in the tubules, especially in the convoluted tubules, the salt and sugar filtered off in the glomerulus is reabsorbed and there is nothing as yet to show that this salt is not reabsorbed in chronic genuine nephrosis. In fact, there is an increased retention of salt in these cases. This retention, as our animal experiments show, is due to the retention of edema through the lowering of colloid osmotic pressure and not to tubular degeneration in the kidney (Ref. 1, 3d paper).

Before I proceed further with this discussion, I want to describe 2 of our most interesting cases of this disease.* One of these was a colleague who had chronic genuine nephrosis in the ordinary form for 5 years. He was investigated at the Rockefeller Institute, was studied by Dr. Berglund of the University of Minnesota, by the late Dr. John Phillips of the Cleveland Clinic, and by myself for a long time. For the first 5 years of his illness his symptoms were

* These cases are to be reviewed in a paper soon to be published by Dr. E. T. Bell and the author.

edema and a moderately severe albuminuria. There was never any hypertension nor any signs of renal insufficiency prior to 1931. There was no hematuria. Everyone concurred that he was the purest type of chronic genuine or lipemic nephrosis until in February, 1931. About this time it was noted that his blood pressure had risen above the normal. During the kidney symposium held at the University of Minnesota in July, 1931, he asked for consultation with Professor Volhard. It was found that his blood pressure was rising and soon after this reached a systolic of 250. His glomerular function, as shown by the kidney function tests, was becoming impaired and Professor Volhard said "This is not chronic genuine nephrosis. He has high blood pressure; he already has signs of renal insufficiency. This is a case of subchronic glomerulonephritis." I never changed my opinion, even then, because red blood cells never came down in his urine until his heart began to fail somewhat later. It is a fact that the blood pressure went up and finally reached extremely high values. It is true that renal insufficiency increased and that he died with a combination of heart failure and true uremia in 1932. Not until the autopsy was the riddle solved and the differences of opinion explained. At that time, we found that the glomerular basement membrane had increased in thickness until it throttled off the circulation through the glomerular capillary loops* (Fig. 2a). Many glomeruli were found to be hyalinized and the corresponding tubules were found to be atrophic. Some of the glomerulotubular units had disappeared and were found replaced by scar tissue. There was no increase in the endothelial or epithelial cells.

We now know, through animal experimentation done by Bell³ and Pedersen, Goldblatt,⁸ Collins,⁴ and Page¹¹ that with this throttling of the circulation, the blood pressure always goes up. It can be seen very easily from the degree of narrowing of the lumen of the capillaries in this case that the flow of blood through his glomeruli must have been reduced very considerably by the narrowing of the capillary lumen.† Moreover, it can be seen that the filtering surface has been reduced very much because of the narrowing of the lumen of the capillaries.‡ The rate of filtration in the glomeruli of this patient must have been reduced to much less than one-fourth the normal. His glomerular filtering function necessarily had to fail because of this throttling process, and metabolites were forced to accumulate because of the impairment of this most important renal function.

* For a description of the kidney in this case, see Bell, E. T., loc. cit.

† If the blood pressure at the arterial and venous ends of a capillary is kept constant and the diameter of the lumen of the tubing reduced to one-half, then according to Poiseuille's law the flow of blood through the capillary is reduced to one-sixteenth of its previous value!

‡ The diameter of the inside of the glomerular capillaries determines exactly the area of the filtering surface in the glomerulus, provided the number and length of these capillaries remains constant. If the diameter is one-half the original capillary diameter and everything else remains constant, the rate of filtration becomes one-half.

He died of uremia just as we would expect him to die, from examination of his kidneys. But in his kidneys, there was not the slightest sign of that type of lesion which is always associated with glomerulonephritis. In other words, there was no endothelial cell proliferation anywhere, no intracapillary fibrils and no epithelial cell proliferation. In glomerulonephritis it is the endothelial cell proliferation, the intracapillary fibrils and the epithelial cell proliferation which cause the throttling of the circulation through the glomerulotubular units and which together with the hyalinization



FIG. 2b —Higher magnification of a small area of the same glomerulus. The great thickening of the basement membrane is well shown. The capillaries in the upper left hand corner are practically completely closed by basement membrane thickening where this section was made. Capillary lumens in the lower left hand corner are open and only moderately narrowed. No increase in endothelial cells or epithelial cells. These photomicrographs were obtained through the courtesy of Dr. E. T. Bell, Professor of Pathology, University of Minnesota.

of glomeruli and tubular atrophy bring about renal insufficiency and uremia. In this case of nephrosis it was the increasing thickening of the basement membrane that brought about the reduced blood flow, ischemia and renal insufficiency.

The other case from the Minneapolis General Hospital service was practically the same in every respect excepting that there always was some hypertension and there were always a few red cells present in the urine. The hydrops in this case was exceptional. The patient was completely incapacitated by an immense anasarca and ascites together with hydrothorax. Histologic examination of

the kidneys showed a small amount of endothelial cell proliferation on careful search. In other words, this case was not quite 100% pure. Thickening of the basement membrane about the glomerular capillary tufts was the outstanding pathologic change in these kidneys. In this case also some of the glomeruli had become completely hyalinized, because blood flow was completely stopped by the thickening of the basement membrane of the glomerular capillaries. The tubules corresponding to the glomeruli with throttled circulation had atrophied. This atrophy as well as the absorption of hyalinized units led to a decrease in size and some pitting of the surface of these kidneys. These cases furnish, in my mind, the best proof that the real and essential pathologic process in chronic lipemic or genuine nephrosis is the change in the basement membrane, its thickening on the one hand, and its increased permeability for small colloid particles on the other. When this thickening increases to the point where the glomerular circulation is throttled, then blood pressure must rise. With the decreased flow of blood through the glomeruli and the decreased filtering surface produced by the marked membrane thickening about the glomerular tufts, renal insufficiency must ensue, and finally uremia must develop and the patient must die in true uremia.

If chronic genuine nephrosis were a distinct pathologic and clinical entity, we should not expect to find its pathologic and clinical characteristics frequently associated with the pathologic and clinical findings of glomerulonephritis. But as an actual matter of fact, cases of pure nephrosis are very rare, whereas cases of glomerulonephritis accompanied by the characteristic symptoms of nephrosis, heavy albuminuria, low serum albumin content of the plasma, marked hydrops, lipemia, and lowered basal rate are really very common. In these cases of subacute and subchronic glomerulonephritis with nephrotic tendency one finds in addition the characteristic symptoms of glomerulonephritis, namely hypertension, hematuria and renal insufficiency. On examining these kidneys one finds not only the endothelial cell and epithelial cell proliferation characteristic of glomerulonephritis but often also the basement membrane changes characteristic of chronic nephrosis. Neither clinically or pathologically is it frequently possible to separate the symptoms and signs characteristic of nephrosis and glomerulonephritis. They are not distinct entities excepting in rare cases but are usually found together. Chronic genuine nephrosis or lipemic nephrosis is only a term that attempts to differentiate as a distinct disease part of the usual picture of subacute and subchronic glomerulonephritis. Therefore it is a part of the picture of glomerulonephritis which occasionally becomes so prominent in the picture that when associated with an absence of the characteristic hypertension and hematuria it seems to be a distinct clinical and pathologic entity until critically examined in the light of all the

facts of symptomatology and pathology. The symptoms and signs of chronic genuine or lipemic nephrosis are only part of the picture of glomerulonephritis. We should learn to think of the symptoms of albuminuria, lowered plasma proteins and hydrops as associated with anatomic and physiologic changes in the ultra-filtration membranes of the glomerulus of the kidney and the hematuria hypertension and renal insufficiency with the obstruction of the glomerular capillaries by endothelial cell proliferation and other obstructive and destructive processes in the glomerulus and with the consequent throttling of the glomerular circulation. We thus approach one of the ideals of medical diagnosis; namely, the reference of symptoms to altered physiology and the correlation of this altered physiology with the findings of pathologic anatomy.

REFERENCES.

- (1.) Barker, M. H., and Kirk, E. J.: *Arch. Int. Med.*, 45, 319, 1930. (2.) Bell, E. T.: *Ann. Int. Med.*, 6, 167, 1932. (3.) Bell, E. T., and Pedersen, A. H.: *Ibid.*, 4, 227, 1931. (4.) Collins, D. A.: *Am. J. Physiol.*, 115, 27, 1936. (5.) Fahr, G., and Kerkhof, A.: *Proc. Soc. Exp. Biol. and Med.*, 30, 1212, 1933; Fahr, G., Kerkhof, A., and Giere, E.: *Ibid.*, 29, 335, 1931. (6.) Fahr, G., Kerkhof, A., and Conklin, C.: *Ibid.*, 28, 718, 1931. (7.) Fishberg, E. H., and A. M.: *Ibid.*, 25, 296, 1928. (8.) Goldblatt, H., Lunch, J., Hauzal, R. F., and Summerville, W. W.: *J. Exp. Med.*, 59, 347, 1934. (9.) Landis, E. M.: *Heart*, 15, 209, 1930. (10.) Leiter, L.: *Proc. Soc. Exp. Biol. and Med.*, 26, 173, 1928. (11.) Page, I. H.: *Am. J. Physiol.*, 112, 166, 1935. (12.) Volhard, F., and Fahr, T.: *Die Brightsche Nierenkrankheit*, Berlin, Julius Springer, 1914.

ABSENCE OF PEPTIC ULCER IN PERNICIOUS ANEMIA.

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THE theories of the etiology of chronic peptic ulcer have been reviewed by numerous writers.² Since hyperchlorhydria has been incriminated as a possible factor in the pathogenesis of chronic peptic ulcer, a determination of the frequency of chronic peptic ulcer in individuals with a known achlorhydria has been undertaken. A review was made of the charts of all patients with pernicious anemia admitted to 9 hospitals* during the period extending from 1921 to 1936. This disease was chosen because of the known absence of free hydrochloric acid in the stomach.⁵

The clinical records of 840 patients with pernicious anemia were examined. Of these, 616 had at least one analysis of gastric content while in the hospital. None of these showed the presence of free

* Permission to use the records of Lakeside Hospital, City Hospital and Mount Sinai Hospital, Cleveland, Beth Israel, Israel Zion, Beth Moses and Mount Sinai Hospitals, New York, and the Cincinnati General Hospital, is gratefully acknowledged.

hydrochloric acid. Sturgis⁵ has shown that achlorhydria is constant in pernicious anemia. Thus it is fair to assume that all the remaining 224 patients or at least a high percentage of them, had achlorhydria.

The following tables are inserted to show that the ages of the patients with pernicious anemia and those with chronic peptic ulcer coincide sufficiently to justify a comparison of the two groups. Table 1 gives the number and sex of 620 of the patients with pernicious anemia in the different age groups. Circumstances made it impossible to secure the age and sex of the other 220 cases.

TABLE 1.—AGE AND SEX DISTRIBUTION OF PATIENTS WITH PERNICIOUS ANEMIA.

	Years.									Total.
	1-10.	11-20.	21-30.	31-40.	41-50.	51-60.	61-70.	71-80.	81-90.	
Number of patients	2	2	16	68	138	215	124	54	1	620
Females	2	1	9	40	81	99	62	27	0	321
Males	0	1	7	28	57	116	62	27	1	299

Table 2³ gives the number and age of a series of patients with chronic peptic ulcer who were studied clinically.

TABLE 2.—AGE DISTRIBUTION OF PATIENTS WITH CHRONIC PEPTIC ULCER.

	Years.							Total.
	0-20.	20-30.	30-40.	40-50.	50-60.	60-70.	70-.	
Number of patients	14	167	261	224	130	66	12	921
Females, 672; males, 249.								

Examination of these tables shows that the highest incidence of pernicious anemia is in the sixth decade, whereas, that of peptic ulcer is in the fourth decade. The distributions differ in that in pernicious anemia there is a sharp peak in the sixth decade, whereas, the curve of peptic ulcer is flatter and still has a high incidence in the fifth decade; 90.8% of the cases of ulcer and 90.1% of the cases of pernicious anemia occur by the end of the sixth decade. Thus it is apparent that in spite of the difference in the peaks of the age incidence, there is sufficient overlap to justify the consideration of peptic ulcer as a disease that could have occurred in the age group of many of the patients with pernicious anemia.

In none of the 840 patients with pernicious anemia was a diagnosis of chronic peptic ulcer made during the time that they were in the hospitals, and in only 2 was there any history at any time of ulcerative lesion of the stomach.

Clinical Notes. One patient, a white male, aged 28, was operated upon for peptic ulcer 10 years before admission to Lakeside Hospital with pernicious anemia. A posterior gastro-enterostomy had been performed and after the operation he had no complaints referable to peptic ulcer. Three

roentgenographic examinations of the gastro-intestinal tract were performed while he was in the hospital for pernicious anemia and a diagnosis of persistent peptic ulcer could not be made upon the basis of clinical or roentgenographic examination.

Another patient, a white male, aged 76, had a bleeding peptic ulcer 2 years before admission to Lakeside Hospital with pernicious anemia. The diagnosis of pernicious anemia was established 1 year before admission to the hospital and 1 year after his peptic ulcer developed. From the time the signs and symptoms of pernicious anemia developed he had no signs or symptoms of peptic ulcer. He was given hydrochloric acid while in the hospital but developed no gastric discomfort. Roentgenograms of the stomach favored the diagnosis of carcinoma rather than gastric ulcer.

Of the remaining 838 patients, 129 had roentgenographic studies of the gastro-intestinal tract. Forty autopsies were performed; 3 on patients who had roentgenographic studies. Neither the roentgenographic studies nor the autopsies revealed the presence of a chronic peptic ulcer. The remaining 669 patients showed no signs or symptoms of existing peptic ulcer, nor gave a history of having had that lesion at any previous time.

Brown¹ gives the incidence of peptic ulcer in the people of North America as 1.3%; Stevens,⁴ as 1.2%. Therefore, in this series there should be, on the basis of these figures, 11 to 17 patients with chronic peptic ulcer. Since none of the patients had peptic ulcer at the time of admission to the hospital with pernicious anemia, and since there is achlorhydria in all true cases of pernicious anemia,⁵ the results of this study indicate that hydrochloric acid in the stomach may be of significance in the pathogenesis and persistence of peptic ulcer. How important this is, cannot be stated on the basis of this study, especially when consideration is given to the frequent absence of pepsin and the antianemic factor from the gastric secretions of patients with pernicious anemia. If it be found, as a result of other surveys of this kind, that chronic peptic ulcer rarely or never develops in a patient with pernicious anemia, it may be safe to infer that at least normal acidity, or perhaps hyperacidity, is one of the conditions necessary for the development of chronic peptic ulcer. As a matter of fact, in another type of anemia, chlorosis, in which there is hyperchlorhydria, the incidence of peptic ulcer is said to be high, but indubitable proof of this on the basis of autopsy findings is wanting. The stomach in pernicious anemia usually shows either mucosal atrophy or chronic atrophic gastritis. It would be mere speculation to attempt to correlate this morphologic change with the absence of peptic ulcer. It is of passing interest, however, that many instances of chronic peptic ulcer are associated with chronic hypertrophic gastritis.

Summary. The records of 840 patients with a well-supported diagnosis of pernicious anemia have been examined. Many of these had proven achlorhydria and it is fair to assume that practically all had this functional disturbance. It is of interest and probably significant that none of these patients had peptic ulcer at the time they had pernicious anemia with its associated achlorhydria.

REFERENCES.

- (1.) Brown, T. R.: Cecil's Textbook of Medicine, 3d ed., Philadelphia, W. B. Saunders Company, p. 723, 1934. (2.) Karsner, H. T.: J. Am. Med. Assn., 85, 1376, 1925; Human Pathology, 4th ed., Philadelphia, J. B. Lippincott Company, p. 635, 1935. (3.) Lynch, R.: Canad. Med. Assn. J., 17, 677, 1927. (4.) Stevens, A. A.: The Practice of Medicine, 3d ed., Philadelphia, W. B. Saunders Company, p. 44, 1932. (5.) Sturgis, C. C., and Isaacs, R.: California and West. Med., 39, 73, 1933.

RADIATION AND CHOLECYSTECTOMY AS THERAPEUTIC PROCEDURES FOR TYPHOID CARRIERS.

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THE chief problem in the treatment of typhoid carriers is the elimination of residual infection from the digestive tract. The intelligent application of therapeutic measures directed toward this end requires a knowledge of the location of the infection. Investigations have, of late, dealt particularly with this aspect of the problem and, chiefly through the use of duodenal drainage as a diagnostic procedure, the infection has usually been located within the biliary tract. That such biliary tract involvement is often limited to the gall bladder is indicated by the fact that cholecystectomy has frequently led to consistently negative feces cultures. Bigelow and Andersen¹ claim to have cured by cholecystectomy all of the 12 carriers whose duodenal fluid contained typhoid organisms, and Hanssen,³ by so treating 5 carriers with infected bile, was similarly successful. Thus, the recovery of infected bile may reasonably be regarded as indication of involvement of the gall bladder and, together with Roentgen evidence of impaired function of that organ or of the presence of stones, warrants consideration of cholecystectomy.

Cholecystectomy, however, is often not feasible, either because of the age or the general condition of the patient or because of his unwillingness to submit to operation. In the treatment of such persons and of those who carry infection in the liver, in the intestine or in the urinary tract, an effective non-surgical procedure is needed. For many years various medical measures have been tried but without success.⁴ The recent report of Gulbrandson² describing the effective use of radiotherapy was, therefore, received with great interest. Treating 12 carriers with small doses of Roentgen-ray directed over the liver, he found 4 free from infection and the remainder with some decrease in the number of typhoid bacilli in

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the feces. In view of such encouraging results further trial of the method seemed desirable.

In the present investigation 22 carriers were studied, 12 of them later being treated by the method of Gulbrandson and 2 by cholecystectomy. In all but 1 who was a urinary carrier, cultures of the duodenal contents before treatment showed typhoid organisms, and gall bladder function was impaired as determined by Roentgen examination. Radiation was entirely ineffective in eradicating the infection. Cholecystectomy, on the other hand, was followed by relief from infection in each instance.

TABLE 1.—FACTS ELICITED FROM THE HISTORIES OF 22 TYPHOID CARRIERS

Patient.	Age.	Sex.	History of typhoid fever.	Interval between infection and identification as carrier.	Length of time known to be carrier.	Cause of identification as carrier.	Number of cases of typhoid fever attributed to carrier.
1	54	M	Yes	None	1 yr.	Hospitalization during disease	0
2	34	M	0	...	3 yrs.	Case in house	1
3	59	F	0	...	2 "	Case in house	2
4	40	M	0	...	2 "	Case in house	1
5	77	F	Yes	28 yrs.	2 "	Case in house	1
6	75	F	2x	35 "	5 "	Case in house	1
7	65	F	0	...	5 "	Case in house	1
8	50	F	0	...	4 "	Case in house	1
9	58	M	Yes	None	11 "	Hospitalization during disease	0
10	37	F	Yes	7 yrs.	1 yr.	Case in house	2
11	62	F	0	...	3 yrs.	Case in house	1
12	51	F	0	...	5 "	Case in house	0
13	43	M	Yes	None	3 "	Hospitalization during disease	0
14	13	F	Yes	None	3 "	Hospitalization during disease	0
15	62	M	Yes	22 yrs.	7 "	Examination as food handler	0
16	43	F	0	...	6 "	Hosp. for G.B. symptoms	0
17	65	F	Yes	27 yrs.	3 "	Hosp. for unrelated illness	0
18	59	F	0	...	10 "	Case in house	1
19	50	F	Yes	None	3 "	Hospitalization during disease	0
20	72	F	Yes	40 yrs.	9 "	Case in house	1
21	23	F	Yes	None	2 mos.	Hospitalization during disease	0
22	47	F	Yes	22 yrs.	3 "	Examination as food handler	0

Subjects of the Investigation. In the summer of 1935, 31 carriers were listed with the Department of Public Health of Philadelphia. Of 22 available for study,* 16 were women (Table 1). The average age was 51.7 years, the youngest being 13 and the oldest, 77 years. Only 13 gave

* Dr. G. E. Johnson, of the Division of Communicable Diseases of the Department of Public Health, very kindly supplied us with the names of the carriers and encouraged them to coöperate.

a history of typhoid fever, and an average of 14 years had elapsed between the illness and discovery of the carrier state. Except for those recognized during hospitalization for their primary illness, the discovery that they were carriers was usually made following the occurrence of a case of typhoid fever in the household. Two subjects, however, were identified as carriers by routine feces examinations when they applied for positions as food handlers, each 22 years after the original illness. In 2 other instances the discovery was made accidentally when the patients were treated for unrelated complaints. The entire group had been registered with the Department of Public Health for an average of 4.1 years; one-half were known to have been responsible each for 1 or more cases of typhoid fever.

Methods of Study and Treatment. In each patient a physical examination was made, a history was taken, and feces and urine were cultured. Duodenal drainage was carried out on those whose feces contained typhoid organisms. Specimens of fasting duodenal fluid and of concentrated "B" bile, obtained following the instillation into the duodenum of warm olive oil, were collected and cultured separately. Roentgen examination of the gall bladder was made in each patient following the oral administration of sodium tetraiodophenolphthalein. All subjects who were not suitable for cholecystectomy or who refused it were given the opportunity of choosing Roentgen ray therapy, and 12 availed themselves of this procedure. The treatment, which duplicated in every important respect the procedures employed by Gulbrandson,² consisted of one or two courses of deep therapy, 330 to 800 R, given at 2- to 4-month intervals.* Treatment was directed over the kidneys or the gall bladder, depending upon the location of the infection as indicated by the previous studies. Following radiation repeated cultures of feces and of urine were made, and also in certain instances a culture of the bile.

Two individuals submitted to surgery, the preliminary studies having been carried out as described. At operation† cultures were made from gall-bladder bile, from the submucous and the muscular coats of the gall bladder and from the interior of calculi removed from the gall bladder. Cultures of feces and of duodenal fluid have been obtained at frequent intervals for a period of 1 to 2 years since operation.

Results of Study and Treatment. In Table 2 are presented the results of Roentgen examination of the gall bladder, of cultures of duodenal fluid and of cultures of feces and urine before therapy was instituted. Positive stool cultures were obtained from 17 of the 22 persons. In all of them Roentgen examination of the gall bladder revealed impaired function, and culture of the duodenal fluid was positive. It was an interesting fact that in 3 a positive culture was obtained only from the concentrated bile. Symptoms suggestive of gall-bladder disease were present in only one-third.

Of the 22 subjects 2 were urinary carriers. In 3 others positive urine cultures were believed to be the result of contamination at the time of collection, and these persons were considered fecal carriers. From 3 no positive cultures were obtained, although these later submitted positive stool specimens to the Health Department.

* Further details of procedure were: For subjects receiving 300 to 650 R, voltage 135 kv.—50 cm. distance—0.25 mm.cu. + 1 mm. al. filtration. For subjects receiving 800 R, voltage 165 kv.—50 cm. distance—0.5 mm.cu. + 2 mm. al. filtration.

† Dr. I. S. Ravdin performed the cholecystectomy in each instance. We are indebted to him for his cooperation.

The results of treatment with Roentgen ray are seen in Table 3. In no instance did cultures of feces or urine become consistently negative after this treatment and culture of duodenal fluid, obtained from 2 patients (Cases 3 and 4), was positive when examined 6 months after conclusion of treatment.

Patients 21 and 22 (Tables 1 and 2) submitted to cholecystectomy after completing the preliminary studies. In both of these the

TABLE 2.—RESULTS OF CULTURES, FINDINGS ON ROENTGEN EXAMINATION OF THE GALL BLADDER AND FREQUENCY OF GALL-BLADDER SYMPTOMS IN 22 TYPHOID CARRIERS.

* Patient.	Cultures.				Roentgen examination of gall bladder.†	Gall-bladder symptoms.
	Feces.	Urine.	Duodenal fluid.*			
			No. 1.	No. 2.		
1	0	+	Neg.	0
2	0	+	0
3	+	0	+	+	Abn.	+
4	+	0	0	+	Abn.	+
5	+	0	Abn.	0
6	+	0	+	+	Abn.	++
7	+	0	+	+	Abn.	
8	+	0	+	+	Abn.	0
9	+	0	0	+	Abn.	0
10	+	+	+	+	Abn.	
11	+	0	Abn.	0
12	+	0	0	+	Abn.	++
13	+	0	+	+	Abn.	0
14	0	0	0	0	Neg.	0
15	0	0	0	0	Abn.	0
16	0	0	0	0	Abn.	+++
17	+	0	Abn.	0
18	+	0	Abn.	0
19	+	+	Abn.	0
20	+	+	Abn.	0
21	+	0	+	+	Abn.	0
22	+	0	+	+	Abn.	+++

* Specimen 1 consisted of fasting, amber bile; Specimen 2 was obtained after olive oil and consisted of concentrated bile.

† Neg. indicates functioning gall bladder; Abn. indicates abnormal function.

TABLE 3.—ROENTGEN RAY THERAPY AND RESULTS OF CULTURES MADE FOLLOWING THIS THERAPY.

Patient.	First Roentgen series, dosage.	Cultures after 1st course of treatment.		Second Roentgen series, dosage.	Cultures after 2d course of treatment.	
		Feces.	Urine.		Feces.	Urine.
1	650 R [†]	0	+			
3	650 R	+	+	650 R	+	0
4	650 R	+	0	600 R	+	0
5	520 R	+	0	600 R	+	0
6	650 R	+	0	650 R	+	0
7	800 R	+	+	800 R	+	0
8	650 R	+	0	650 R	+	+
9	800 R	+	0			
10	800 R	+	0			
11	800 R	+	0			
12	330 R	+	0			
13	800 R	+	0			

* Treatment was directed over both kidneys in this patient; in others over the gall bladder.

culture of duodenal fluid prior to operation was positive and Roentgen examination of the gall bladder revealed impaired function. At operation positive cultures were obtained from gall-bladder bile, from the mucous membrane of the gall bladder and from the interior of calculi. In Patient 22 a culture from the muscular coat was also positive. After operation cultures of the duodenal fluid and of feces have been negative in each instance from the third post-operative day to 13 months after operation, examinations having been made at intervals of approximately 3 months during this time.

Conclusions. 1. Evidence of involvement of the gall bladder was obtained either by duodenal drainage or by Roentgen examination in all of 17 typhoid carriers whose stool cultures were positive. Infection was demonstrated only in the urinary tract in 2 others.

2. Irradiation directed over the gall bladder in 12 carriers failed to destroy the organisms as judged by persistently positive cultures of bile and feces. This therapy was also ineffective in the one urinary carrier treated.

3. Surgical removal of the gall bladder in 2 carriers permanently removed the focus of typhoid infection.

REFERENCES.

- (1.) Bigelow, G. H., and Andersen, G. W.: J. Am. Med. Assn., 101, 348, 1933.
(2.) Gulbrandson, L.: Illinois Med. J., 67, 262, 1935. (3.) Hanssen, E. G.: New York State J. Med., 35, 1206, 1935. (4.) Stertenbrink, A.: Ergebn. d. inn. Med. u. Kinderh., 33, 143, 1928.

ACUTE PANCREATITIS: A MEDICAL PROBLEM.*

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DESPITE the fact that the surgical treatment of acute pancreatitis has not appreciably lessened the mortality rate in the past 50 years, the dominant medical opinion today concerning the treatment of this disease is that it remains a serious surgical problem. There is, however, considerable disagreement as to the best surgical approach. Some incise the pancreatic capsule, others drain the common duct; some drain the gall bladder, others remove it; still others do various combinations of the above. Similar confusion exists as to the optimum operative time. Whereas some authorities believe that

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the deplorably high death rate can be lowered only by immediate operation, others recommend delaying the operation for several hours until the initial shock has passed. Still others advise the so-called interval operation in which surgery is deferred for from 4 to 8 days. The confusion still extant as to the relative merits of the various operative procedures and as to the optimum operative time undoubtedly remains unresolved because of the monotonously high mortality rate common to all of them.

The most recent tendency in the treatment of acute pancreatitis, abstinence from operation, represents a radical departure from the generally accepted surgical attack on the disease. This, on first thought, appears to confuse the problem further, but may ultimately clarify and simplify it. Hartlieb⁷ is absolutely opposed to the prevailing idea of surgical intervention. Whereas he had in years past operated on 23 patients with 12 deaths, the usual mortality rate, in a later group of 7 cases, treated expectantly, 5 recovered and 2 died. Nordmann¹¹ treated 9 patients with acute pancreatitis conservatively with 7 recoveries. Mikkelsen¹⁰ reported conservative treatment of 39 cases of acute pancreatitis with the amazing mortality rate of only 7.5%. He believes that it is irrational to incise the pancreatic capsule, as incision of such a peritoneal covering cannot possibly relieve secretory tension. It is Walzel's¹⁴ opinion that operation should only be considered in those cases in which a surgical condition, such as a ruptured peptic ulcer, cannot definitely be excluded and that if, at operation, an acute pancreatitis is found, the abdomen should be closed. Hofhauser⁸ stresses the importance of differentiating between necrosis of the gall bladder and necrosis of the pancreas because the treatment is surgical in the former and conservative in the latter. Doubt that operation can appreciably lessen the necrosis of pancreatic tissue with its attendant release of toxins is expressed by Arehibald and Kaufman.¹ In their experiments with acute pancreatitis in dogs, Cook and Whipple⁴ showed that the pancreas has unusual power of recuperation if it is let alone behind a closed peritoneal cavity.

Data. The above reports stimulated us to analyze the records of patients with acute pancreatitis who were admitted to this hospital during the past 3 years (Table 1). The 16 unselected cases were comprised of 10 males and 6 females. The youngest patient was 32 years of age and the oldest 70 (average 46). Patients 1 to 4 were operated on either on the first or second day of admission, with 3 deaths and 1 recovery. Patients 5 to 8 were operated on from 8 to 13 days after admission and after the acute symptoms had completely subsided. These patients were operated on only because mild signs of gall bladder disease, such as tenderness in the right upper quadrant, persisted. Of these, all showed evidence of acute hemorrhagic pancreatitis on laparotomy. In only 1 was the capsule incised. In the remaining 4 cholecystectomy was performed. The

operation in no case was deemed essential for the acute pancreatitis itself; in fact, as stated above, the symptoms of shock, abdominal pain, vomiting and temperature had completely disappeared. From the standpoint of acute pancreatitis, these cases are considered as non-operative. Of Patients 9 to 16 who were not operated on at all, 4 recovered and 4 died. The deaths occurred in Case 11, a man of 70, the oldest patient in the group; in Case 14, who had anuria for 24 hours and a urea nitrogen of 100 mg. per 100 cc. of blood; and in Case 15, who had anuria for 2 days and necropsy

TABLE 1.—RESULTS IN 16 CASES OF PANCREATITIS.

Case.	Sex.	Age (yrs).	Oper. No. days after admission.	Type of operation.	Oper. findings.	Result.	Autopsy.	Dias-tase.	Ser. lipase.	Hyper-glycemia mg. per cent.
1	F.	42	1	G. B. drained	Sero-sanguinous fluid, fat necrosis	Died	+	352
2	M.	49	Same	G. B. drained	Hem. panc., fat necrosis, gall bladder stone	Died	+	1:128	..	260
3	F.	36	1	Cap. incised	Fat necrosis, edem. and hem. pancreatitis	Died	240
4	M.	41	Same	Cap. incised	Edem. pancreatitis, free sang fluid	Recovered				
5	M.	43	10	G. B. removed	Fat necrosis, hem. fluid edem. panc.	Recovered	..	1:200	..	190
6	M.	59	8	G. B. removed	Cholelithiasis, hem. pancreatitis, fat necrosis	Recovered	280
7	F.	53	12	G. B. removed	Cholelithiasis, fat necrosis, hem. fluid	Recovered	..	1:256	..	330
8	F.	42	13	panc. incised G. B. removed	Gangrenous cholecystitis; hem. pancreatitis	Recovered	..	1:128	..	210
9	F.	38	10	G. B. removed	Calc. cholecystitis, fat necrosis, free fluid	Recovered				
10	M.	44	Recovered	+	1:512	..	195
11	M.	70	Died	+			
12	M.	46	Recovered	..	1:256		
13	F.	45	Recovered	+	1:1024	..	310
14	M.	40	Died	+	200
15	M.	64	Died	+			
16	M.	32	Recovered	..	1:521	2.6	

findings of a severe and extensive nephrosis. The criteria for the diagnosis of acute pancreatitis in the 4 patients who recovered without operation were the typical clinical features plus markedly elevated urinary amylase estimations. The clinical features alluded to conformed to a rather characteristic pattern of severe right upper quadrant pain which radiated to the left, marked distention, vomiting, shock and a mild elevation of temperature. In 3 patients we were able to demonstrate a small amount of fluid in the chest, presumably due to a pleural reaction by extension from the pancreas. Mention should be made that those cases not operated on, or operated on late, were in no way milder clinically than those on whom operation was performed early. When the results in Pa-

tients 5 to 16 are grouped together under the non-operative treatment of this disease, it will be seen that 9 of the 12 patients recovered, whereas 3 of the 4 patients subjected to the additional burden of an early operation succumbed.

The idea that surgery in acute hemorrhagic pancreatitis should be abandoned coincides with the recent interesting work by Duff and Rich¹² on the pathogenesis of this disease. They found in 13 of 24 pancreatic glands studied that the disease is due to obstruction of the pancreatic ducts by a metaplasia of the ductal epithelium. This metaplasia, patchy in distribution, is a localized proliferation which projects into the ducts and partially or completely occludes their lumina. The ductules and acini immediately behind the obstructed ducts become greatly distended and their thinned out walls become easy to rupture. The cause of acute hemorrhagic pancreatitis resides often, therefore, in the gland itself and not in factors external to it such as gall stones, spasm of the sphincter of Oddi or lymphatic infection. If this view of the pathogenesis of acute pancreatitis is correct, it can readily be seen that the surgeon could not possibly know, considering the scattered nature of the lesion, in which lobules the obstructed ducts may be, and even if he did, the necessary multiple incisions into individual lobules could only increase the hazards of necrosis.

In any discussion of treatment a few words about diagnosis are in place. As will be seen in Table 1, 8 estimations of urinary diastase were made, all of which were definitely elevated. We regard this test, along with Foged,⁶ Rost,¹³ McCaughan⁹ and others, as exceedingly helpful. Its ease of performance should lead to its more general use in all cases of suspected acute pancreatitis. It is true that elevation of the urinary diastase has been observed in kidney disease, diabetes mellitus and peptic ulcer, but in none of these conditions are more than moderate increases encountered. The normal index of diastasuria oscillates between 6 and 30 units. Table 1 shows how much higher the figures rise in acute pancreatitis. Even those who do not think the test specific admit its value when interpreted in the light of clinical findings.

Serum lipase estimation, a relatively new test, may supersede the diastase test in accuracy as a valuable diagnostic aid in acute pancreatitis. Cherry and Crandall⁵ showed that lipase in normal sera exists in minute amounts and that it is increased markedly after ligation of the pancreatic ducts. Comfort and Osterberg⁷ think the increase in serum lipase good evidence of disturbed pancreatic function especially when correlated with the clinical picture. According to Bernhard,² the increase in serum lipase subsides more slowly than the increase in urinary diastase. In our own series, we performed the test only once with, we believe, a correct result.

The point we wish to stress is that a diagnosis of acute pancreatitis can be made without operation. The clinical aspects alone are

often unmistakable. However, when these are insufficiently clear, we have now two fairly reliable tests which can be easily and quickly done, to help clarify the diagnosis. We believe an early diagnosis important so that surgery may be avoided.

Summary and Conclusions. The operative mortality of acute hemorrhagic pancreatitis remains uniformly high, which probably accounts for the existing disagreement concerning the best operative approach and the optimum operative time. Recent reports on the non-operative treatment of this disease show a lower mortality rate. We present 16 cases of acute pancreatitis in which 4 were operated on with 1 recovery and 12 were not operated on for the pancreatitis with 9 recoveries. Diastase and lipase estimations are of considerable value in the diagnosis of suspected pancreatitis. It is felt that further trial with conservative therapy in acute hemorrhagic pancreatitis is warranted.

REFERENCES.

- (1.) Archibald, E. W., and Kaufman, M.: Dean Lewis, Practice of Surgery, 7, 1, 1929, Hagerstown, Md., W. F. Prior Company, Inc.
- (2.) Bernhard, F.: Klin. Wehnschr., 12, 221, 1933.
- (3.) Comfort, M. W., and Osterberg, A. E.: J. Lab. and Clin. Med., 20, 271, 1934.
- (4.) Cooke, J. V., and Whipple, G. H.: J. Exp. Med., 28, 223, 1918.
- (5.) Crandall, L. A.: Am. J. Digest. Dis. and Nutr., 2, 230, 1935.
- (6.) Foged, J.: Am. J. Surg., 27, 439, 1935.
- (7.) Hartlieb, G.: Beitr. z. klin. Chir., 157, 539, 1933.
- (8.) Hofhauser, J.: Arch. f. klin. Chir., 182, 443, 1935.
- (9.) McCaughan, J. M.: Surg., Gynec. and Obst., 59, 598, 1934.
- (10.) Mikkelsen, O.: Acta Chir. Scandinav., 75, 373, 1934.
- (11.) Nordmann, O.: Chirurg., 1, 721, 1929.
- (12.) Rich, A. R., and Duff, G. L.: Bull. Johns Hopkins Hosp., 58, 212, 1936.
- (13.) Rost, F.: Münch. med. Wehnschr., 80, 1961, 1933.
- (14.) Walzel, P.: Med. Klin., 30, 1516, 1934.

CLINICAL OBSERVATIONS ON THE TREATMENT OF PNEUMONIA AND EMPYEMA BY SOME QUININE DERIVATIVES, ESPECIALLY HYDROXYETHYLAPOCUPREINE.*

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In a previous report⁹ we indicated that hydroxyethylapocupreine was of considerable interest because of its low toxicity for mice and its relatively high antipneumococcic power, as compared with other

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quinine derivatives. An experimental study² in dogs was of further interest in regard to hydroxyethylapocupreine in that this compound was found to be free from damaging effects on the retina, and therefore did not produce blindness. On the other hand, optochin and ethylapocupreine did cause blindness in these experiments, while apocupreine did not. It is a well known clinical fact that the use of optochin in the treatment of pneumonia cases has been associated at times with the temporary loss of vision. It is this untoward result that is probably responsible for this interesting chemical being withdrawn from the therapy of pneumonia by most physicians. In the past, we have seen a moderate number of early pneumonia cases treated with optochin in the usual small therapeutic dosage with the result that the mild cases recovered while the toxic cases did not appear to be affected. The latter, when observations were made, were usually the positive blood culture cases. Moore and Chesney¹⁰ and Solis-Cohen¹¹ many years ago made careful experimental and clinical studies on optochin and quinine. We refer the reader to their work. In the years 1930-1931 we decided it would be of value to prove whether optochin in large dosage did have the power of favorably altering the course of toxic pneumonia cases. We observed 4 patients. All had positive blood cultures, both in the broth flasks and on the blood agar plates. The highest colony counts, respectively, were 6, 8, 45 and 260. These cases were given 60 gr. of optochin per day for 3 to 5 days. They all recovered. Two (cases with 6 and 260 colonies) showed no visual disturbance, while the other 2 developed blindness from which they recovered good vision in the course of 2 months. Further, at this time, we also treated a single case of pneumococcic endocarditis, which as far as we know is invariably fatal, with very large doses of optochin. This patient had, as is common for practically all cases of pneumococcic endocarditis, pneumococci in the blood with high colony counts. He was given 90 gr. of optochin per day for 3 days. The chemical was discontinued for 2 or 3 days and then given again in the same dosage for the same length of time. This was repeated four times so that the patient received about 1000 gr. He never showed any visual disturbance, indicating that the blindness due to the quinine derivatives is probably an idiosyncrasy. The blood cultures would be sterile after the second day of treatment, but the organism returned when the optochin was stopped. The patient died on the 35th day of his illness and the autopsy confirmed the pneumococcic endocarditis.

Later, in 1932-1934, we treated a much larger series of positive blood culture cases with ethylapocupreine. The dosage was from 40 to 60 gr. per day and it was continued from 3 to 4 days. Naturally in dealing with positive blood culture cases there were many of the total number that did not show the pneumococci in the blood until after the fourth day of the disease. Negative blood culture

cases were not treated. In this group of 24 cases there were 10 recoveries and of the cases which recovered, 4 showed high colony counts on the blood agar plate, 15, 21, 32 and 377, respectively. Five out of the 24 cases developed blindness. One of this group of 5 died, while the remaining 4 regained good vision in periods varying from 1 to 3 months.

From these clinical observations with optochin and ethylapocupreine we were impressed with two facts. The first one was that the visual disturbance, which in our cases was total blindness for several days followed by partial loss of vision for a number of weeks but with ultimately good vision returning, renders such chemical compounds absolutely impossible to use in clinical medicine. The second fact was that we had very suggestive evidence that the blood stream could be freed from pneumococci and that some of the patients recovered from their pneumonia if a sufficiently large enough dosage of chemical be given. The desirability, therefore, of developing a quinine derivative devoid of the visual damaging factor but with the pneumococcidal power not impaired naturally was obvious.

For part of the winter of 1934-1935 we used apocupreine which by animal and *in vitro* tests had very little toxicity and fair anti-pneumococci power. This chemical compound was discarded after a few months' trial on 20 cases of pneumonia. We saw practically no evidence in the positive blood culture group that were treated in this series that apocupreine had any effect on the course of the disease. This preparation, however, produced no blindness and could be given in very large dosage, 120 gr. per day for 4 or 5 days. It is possible that this chemical is altered in the human body and its antipneumococcic power is subsequently lost.

Hydroxyethylapocupreine was first used in the treatment of pneumonia cases in 1935-1936. It was given in capsule by mouth in divided doses, and the usual dose at that time was 60 gr. per day. A few cases had more. It was soon noted that no evidence of visual disturbance was to be observed, and in the following year this finding has been confirmed. After treating about 200 cases there has not been a single example of visual disturbance, which agrees with our experimental study on dogs previously mentioned. In the first year there was no nausea or vomiting associated with the use of the hydroxyethylapoquinine, and on only one occasion did ringing of the ears appear, after 600 gr. had been taken. In the year 1936-1937, however, a good deal of nausea and vomiting was seen, but we feel fairly certain that these symptoms were characteristic of the epidemic influenzal infection which was prevalent, as frequently the non-chemically treated cases had nausea and vomiting, usually during the first few days of illness. It is quite true that in the presence of nausea and vomiting most medication by mouth will increase these disagreeable symptoms, and this undoubtedly hap-

pened during the past year with our cases of pneumonia treated with the chemical.

The dosage of hydroxyethylapocupreine during the past year (1936-1937) was very much larger than during the first year (1935-1936). This was partly due to the fact that in the first year the chemists at the Mellon Institute were able to get only a 5% yield in production. However, in the summer of 1936, Dr. Butler increased the yield of hydroxyethylapocupreine from quinine by a new process to 40%. Consequently for the past year we have had an adequate amount to use, and accordingly increased the dosage. Fifteen grains every 3 hours, day and night, has been the routine dosage. From 400 to 900 gr. in the course of a week has been frequently given. During the past year we have given intravenous injections of the chemical to a certain number of the more toxic cases. Fifteen grains in 50 to 75 cc. of distilled water can be injected into the vein safely every 3 or 4 hours. We have frequently given 60 gr. by mouth and 90 gr. intravenously per day in divided doses.

Hydroxyethylapocupreine in the form of the dihydrochloride was first used, but this salt is quite acid and probably accounted for the almost constant thrombosis of the veins at the point of injection. In the past few weeks we have substituted the monohydrochloride which is almost a neutral solution and in a limited experience have seen no local thrombosis of the veins of the arm. The monohydrochloride solution is readily made by dissolving 15 gr. (1 gm.) of the hydroxyethylapocupreine dihydrochloride in 100 cc. of distilled water (a 1% solution) and to this solution adding slowly about 2.5 cc. of normal sodium hydrate. The solution becomes milky at first but clears when the monohydrochloride stage is reached.

No intravenous injections were used in the first year (1935-1936) and this fact in addition to the small dosage given by mouth probably accounts for the greater mortality seen in our first than in the second year.

There was only one instance when a reaction associated with a fall in blood pressure followed the intravenous injection. We have so far met with no example of a definite alarming allergic response to the hydroxyethylapocupreine. Ringing in the ears was noted once during the first year and twice this year in patients who had taken large doses. It was only slight and stopped with the discontinuance of the chemical. After large dosage in a few individuals we have noted a fine skin eruption which may be due to the hydroxyethylapocupreine. It caused no discomfort and was very temporary in character. We do not believe the nausea and vomiting seen at times this year can be a manifestation of drug sensitivity, as it was not present last year and the symptoms were frequently noted in non-chemically treated cases this year. Of course, there may be cases that will not be able to take this chemical. Certainly, it appears to be entirely free from any of the untoward reactions

that are associated with quinine, optochin and ethylapocupreine, even when the hydroxyethylapocupreine is given in much larger doses.

It is our belief that the chemical should be taken by mouth as soon after the chill or onset as possible and continued as long as necessary. The intravenous method is for the more toxic cases, especially those with positive blood cultures. Probably very little benefit can be hoped for in cases after the fourth day of the disease as is true for specific serum.

TABLE 1.—MORTALITY FIGURES.

	Treated cases.		Untreated cases.	
1935-1936	46	17 deaths (37%)	48	20 deaths (42%)
1936-1937	100	27 " (27%)	46	29 " (63%)
1935-1937	146	44 " (30%)	94	49 " (52%)

Mortality According to Types.

		Treated cases.		Untreated cases.	
Types.			Deaths.		Deaths.
1935-1936	I	4	2 (50%)	8	1 (12%)
	II	10	6 (60%)	3	2 (67%)
	III	4	3 (75%)	7	6 (86%)
	Group IV	28	6 (21%)	30	11 (37%)
1936-1937	I	13	5 (38%)	4	2 (50%)
	II	19	8 (42%)	1	1 (100%)
	III	15	9 (60%)	8	7 (87%)
	Group IV	48	5 (10%)	12	7 (58%)
Unknown		5	0 (0%)	21	12 (57%)

Mortality as to Types in the 44 Deaths in Treated Cases.

1935-1937	Type I	7 deaths (16%)
	II	14 " (32%)
	III	12 " (27%)
	Group IV	11 " (25%)

(Types IV, VII, VIII, X (2), XVIII, XX, XXVI, Group IV unclassified. (3).)

In the above table the mortality figures for the first year, 1935-1936, show little difference between the treated and non-treated. In this first year, the untreated cases were frequently early cases, while in the year 1936-1937 the untreated cases were nearly all beyond the fourth day of the disease. Therefore, they are not to be considered as true control cases. The mortality in the second year is lower than the first. (The normal mortality in our hospital ward for 100 non-specifically treated cases has been about 45%. In 1935, Pittsburgh had 161 deaths from pneumonia per 100,000; in 1936, 193 per 100,000; and 1937 will probably be higher due to the epidemic of influenza, as in the first 4 months of the year 1937 there were 84 more deaths from pneumonia and influenza than during the same period of the previous year.) The mortality according to types shows that the three fixed types are the highest with a lowering of the figures during the past year. The cases in regard

to type mortality were too few in the first year to be accurate. The large number of unknown types in the untreated series of 1936-1937 was due to a combination of the following circumstances: no sputum, late cases, a few outside cases and cases on other services.

TABLE 2.—CASES TREATED BUT NOT INCLUDED IN OUR LISTS.

1. Five died with insufficient treatment, 3 being less than 1 day and 2 less than 2 days. Of the latter, 1 had coronary thrombosis while the other had mitral stenosis with fibrillation and circulatory failure.
2. There were 25 in which the final diagnosis of pneumonia could not be made: 22 recovered, 3 died, deaths being due to lung abscess, coronary thrombosis and bronchogenic carcinoma of lung.
3. Four postoperative pneumonias were treated, with 3 recoveries and 1 death.
4. No children were included.

Some of the recovered cases of Section 2 were patients to whom the chemical was given almost immediately or within a very few hours after the chill. Prompt cessation of their symptoms and absence of signs which included Roentgen rays for all hospital cases made a positive diagnosis of pneumonia impossible. This group, however, represents a most interesting picture and there should be no difficulty in the future in collecting many cases where the chemical has been given very shortly after the chill. This will be applicable to hospital pneumonia only occasionally, but many cases in the homes are seen by their physician at the earliest stages of the disease and this group should be very instructive.

TABLE 3.—ANALYSIS OF SOME OF THE 27 FATAL TREATED CASES (1936-1937).

Staphylococcus empyema and bacteremia	1
Streptococcus hemolyticus bacteremia	1
Delirium tremens	2
Late cases—sixth and eighth days	2
Sudden death—end of third day; temp., 98.8° F.; pulse, 100 (Coronary ?)	1
Pneumonia associated with severe epidemic influenza	6
	<hr/> 13

This table is given not with the intention of excusing the mortality during the past year but to call attention to the fact that mixed infection in our opinion undoubtedly played a part in the mortality. Pneumococcus was present in all of the fatal cases in addition.

TABLE 4.—INCIDENCE OF H. INFLUENZÆ AND STREP. HÆMOLYTICUS IN SPUTUM.

Month.	Sputum specimens.	H. influenzæ.	Strep. hæm.	H. infl. and Strep. hæm.
December, 1936	22	1 (4%)	0	0
January, 1937	44	18 (41%)	9 (20%)	3
February, 1937	23	7 (30%)	5 (21%)	1
March, 1937	25	15 (60%)	7 (28%)	4
April, 1937	16	8 (50%)	4 (25%)	1

The epidemic influenza appeared during the last week of December, 1936. The above table indicates the increase in the *H. influenzæ*

and the *Strep. hemolyticus* during the past winter. This was done by making blood agar and chocolate agar plates from the sputum, and the above records are from cultures, not from direct smears of the sputum. The incidence of both of these organisms is far above our normal findings for a non-epidemic year. The chart adds further proof of mixed infection in the pneumonias of the past winter.

TABLE 5.—ANALYSIS OF PNEUMOCOCCUS TYPING.

Type.	1935-1936.		1936-1937.	
	No. of cases.	Per cent.	No. of cases.	Per cent.
I	15	15.0	17	14.1
II	13	13.0	20	16.6
III	14	14.0	23	19.1
IV	3	3.3	5	4.8
V	5	4.8
VI	1	1.1	1	0.9
VII	7	7.7	7	6.7
VIII	9	9.9	6	5.7
IX	3	3.3	1	0.9
X	5	5.5	3	2.8
XI	2	2.2		
XII	1	1.1	2	1.9
XIII	1	1.1	1	0.9
XIV	2	2.2	1	0.9
XV				
XVI				
XVII				
XVIII	2	2.2	1	0.9
XIX	1	1.1	1	0.9
XX	3	3.3	1	0.9
XXI				
XXII	1	0.9
XXIII				
XXIV	1	0.9
XXV	6	6.6	1	0.9
XXVI	1	1.1		
XXVII	1	1.1	2	1.9
XXVIII	1	1.1	1	0.9
XXIX	2	1.9
XXX				
XXXI	1	0.9
XXXII				
(Group IV unclassified)	9	9.9	16	13.3
	100		120	

The small number of Type I cases has been noted for several years in Pittsburgh in all laboratories where typing has been done. It is interesting that Type III has been so relatively frequent during the past 2 years.

There was a definite difference in the mortality of the treated and untreated series, both in the negative and positive blood culture cases in the combined years of 1935-1937. The untreated series are not true controls, in that they were late cases, especially during the year 1936-1937. We would emphasize that 19 treated cases with positive blood cultures recovered, while there were only 4

TABLE 6.—ANALYSIS OF BLOOD CULTURES (1935-1936).

B. C.	Treated cases.				Untreated cases.			
	Cases.	D.	R.	Mortality.	Cases.	D.	R.	Mortality.
Neg. . . .	24	3	21	12%	36	11	25	31%
Pos. . . .	22	14	8	64%	12	9	3	75%
	(48%)				(25%)			
1936-1937.								
Neg. . . .	63	10	53	16%	27	12	15	44%
Pos. . . .	25	14	11	56%	14	13	1	93%
	(28%)				(34%)			
Combined Figures (1935-1937).								
Neg. . . .	87	13	74	15%	63	23	40	36%
Pos. . . .	47	28	19	59%	26	22	4	85%
	(35%)				(29%)			

recoveries in the non-treated group. The 4 untreated positive blood culture cases that recovered (Types I (2), II, XXV) had no colonies on the blood agar plate, the pneumococci being present only in the broth flasks. The high mortality figures for the negative blood culture cases in the untreated group is difficult to explain, but two factors may play a part: (1) Failure to take blood cultures up to the time of death (some of these cases were not under control) and

TABLE 7.—ANALYSIS OF 19 POSITIVE BLOOD CULTURES IN RECOVERED CASES (1935-1936).

Name.	Type.	No. pos. B. C.	Colony counts.
Cirelli	II	1	0
Johnston	VIII	2	8, 4
Evans	VIII	5	2, 0, 2, 1, 0,
Yeckley	X	2	0, 0
Hanley	VIII	2	0, 0
Dugan	XX	3	1, 38, 0
McKinney	XII	2	0, 0
McDaniel	VIII	1	0

1936-1937.

Rankin	I	1	0
Ferguson	VIII	1	0
Robertson	IV	1	0
Gillespie	Group IV	1	0
Cain	II	1	0
Fabiani	II	1	0
White	VIII	1	0
Deferris	IX	1	0
Bianco	V	5	1, 418, 260, 0, 4
Culver	VII	3	231, broth pos. twice but no plates made
Patton	II	13	54, 4, 4, 48, 67, 28, 10, 58, 10, 0, 5, 2, 0

thus classifying cases in the negative group when they really may have had a bacteremia; (2) during the past winter with the large amount of mixed infection, prolonged clinical courses from 12 to 20 days were not infrequent and more cases were noted dying with negative blood cultures than formerly.

There were 4 instances in the above 19 recovered positive blood

culture cases in which the colony counts were above 15 per cubic centimeter, while 9 showed multiple positive cultures. In the above chart 0 means that there were no colonies on the plate, but the broth was positive. It is our belief that the mortality figure in 100 chemically treated positive blood culture cases (cases not later than the fourth day) should give a fairly accurate idea as to the value of this method of therapy. This could be controlled further by comparing a similar series of positive blood culture cases, with and without specific serum, from other hospitals in Pittsburgh.

TABLE 8.—MORTALITY FIGURES ACCORDING TO DAY OF DISEASE WHEN FIRST TREATED (1935-1937).

Day.	Cases.	Deaths.	Positive B. C.		Types I, II, III.	
			No.	Deaths.	No.	Deaths.
First . . .	50	13 (26%)	13 (26%)	4 (31%)	16 (32%)	8 (50%)
Second . . .	50	17 (34%)	16 (32%)	11 (69%)	27 (54%)	14 (51%)
Third . . .	21	1 (4.7%)	4 (19%)	1 (25%)	8 (38%)	1 (12%)
Fourth . . .	20	10 (50%)	12 (60%)	9 (75%)	12 (60%)	8 (67%)
Fifth plus . .	5	3 (60%)	2 (40%)	2 (100%)	2 (40%)	2 (100%)

77% of the 13 fatal cases treated on first day died within 5 days of onset.

23% of the 17 fatal cases treated on second day died within 5 days of onset.

We would call attention to the low mortality of the cases first treated on the third day. The 21 cases included 8 in 1935-1936 and 13 in 1936-1937. The single death occurred in the last year. The percentage of the three fixed types (the more virulent forms) in the third-day group was higher than those cases of the first day, while the positive blood culture percentage was somewhat lower than the first-day cases. The duration of the pneumonia in the fatal cases treated on the second day was considerably longer than for those treated on the first day. It is possible that there may be a common explanation for the low mortality in the third day and the difference in duration of the disease in the fatal cases of the first and second days. This should be easily proved during the coming year when larger numbers are available.

We have previously mentioned that mixed infection was present to a considerable extent during the past winter and have shown some bacteriologic evidence as indicated by the cultures made from the sputum of the pneumonia cases. Autopsy findings this year confirmed the clinical fact that we have had epidemic influenza as a background for the pneumonias. Although much less in number, practically all of the autopsy findings of the 1918 epidemic were reproduced this past winter. Three cases showed typical Zenker's degeneration of muscle as was so accurately described by Klotz⁵ in his pathologic studies of the influenza epidemic in Pittsburgh in 1918. The wet hemorrhagic lungs were fairly frequently observed and delayed resolution with small multiple abscess formation was also seen.

From the clinical side several unusual features of the pneumonias were noted. At the onset nausea and vomiting was not only common but it was very severe in many cases and at times persisted

for 3 or 4 days. This condition was not seen in 1935-1936. An occasional cyanotic case of the 1918 type was encountered but we saw no evidence of the leukopenic state that was so frequent in the previous epidemic. A few low white counts were noted in the pneumonias this year, but they were usually found in chronic alcoholics. The delay in the appearance of typical signs of consolidation, prolonged periods of depressed breathing over the involved lobe, and the presence of widely diffused râles through the lung were also noteworthy.

Probably one of the most characteristic features of the pneumonias this year was the prolongation of the febrile course and signs of delay in resolution of the process. In 1935-1936, 13% of the recovered treated cases showed fever for over 15 days, while in 1936-1937 the percentage was 22. In the untreated recovered group, during the first year 7% had fever for over 15 days, but in the second year 47% of the cases showed a prolonged febrile reaction.

It might also be added that streptococcic hæmolyticus empyema in adults, following a pneumonic course, has been more in evidence than our records would indicate for many years. We hope that the influenza epidemic of the past winter represents the peak of the infection and not a forerunner of the coming year, as its virulence next year would need very little enhancing to cause a most serious disease.

In 1922, Gralka⁴ reported the first case of pneumococcic empyema treated by the injection of optochin into the pleural sac. His cases were in children, and in fact all of the subsequent literature on this problem deals with empyema in children. Gralka's first case occurred in 1920. Kolmer and Sands⁶ drew attention to this subject in 1921 when they reported on some experimental studies on empyema in guinea pigs which were treated effectively by injections of optochin. Woringe,¹² Leitner,⁷ Bussel and Hirszfeld,¹ Lowenburg,⁸ Edeiken³ and others have reported that optochin was of value in the treatment of empyema in children. The total number of cases has not been large and one is surprised that this method of treatment has received so little attention. We have not seen any record of treatment of pneumococcic empyema in the adult by this method. The fear of visual disturbance by optochin and the fact that recognized empyema in the adult carries a low mortality with the usual surgical methods of approach probably account for the lack of interest in the chemical therapy for this condition.

For the past 7 years we have treated most of our empyemas with one of the quinine derivatives, although in the first 2 years when we used optochin in a dilution of 1 to 400, tubes were inserted between the ribs into the empyema sac and the optochin solution was left in the cavity. This was repeated daily. The duration of the empyema was shortened considerably. Ethylapocupreine was used in the same way at first, but later we injected a 0.5% solution.

never more than 100 cc., into the pleural sac after the aspiration of as much of the purulent fluid as possible. This was done 3 or 4 times in the course of a week or 10 days. Only occasionally was it necessary to put tubes into the cavity. It was this closed method that was used by the previous writers mentioned above. The dosage of optochin or ethylapocupreine was far below the toxic dose which produces blindness and the method was therefore safe. We treated but a small number of cases in this manner, 2 or 3 per year.

However, since 1935 we have injected the hydroxyethylapocupreine in a 1 or 2% solution and in this period have seen about 15 cases of empyema. It has been very effective in our hands. The course of the empyema is shortened, at times to 1 or 2 weeks, and the method is much easier for the patient, in that there is no rib resection or introduction of tubes between the ribs into the pleural sac. We have had 1 case of empyema on the left side with a pericardial rub which persisted for 5 days, but which disappeared as did the empyema in the course of 10 days after 4 injections of 100 cc. of a 2% hydroxyethylapocupreine. It was a Type I infection.

Our procedure is as follows: Aspirate the pus and prove that it is pneumococcus by cultural methods, as this chemical does not affect the streptococcus. Inject 100 cc. of a 1 or 2% solution of the drug after removing as much of the empyema pus as possible. Obviously, if only 50 cc. of pus is removed, the amount of the chemical solution is reduced to that figure. On the following day repeat the injection and make the third and fourth injection if indicated by a rise of the temperature. If the injections of chemical are too many days apart, with a subsequent return of fever, the empyema may persist as it has done in 2 cases that we watched. These are the only ones where the empyema did not end in the course of a week or 10 days. The injections must be made frequently during the first week. We have noted that in the pus, removed after the chemical has been injected, the pneumococci can be seen in the smears and will show the "quellung" phenomenon but they will not grow when transplanted to media. The pus is therefore sterile. This observation we have frequently noted. It is not at all likely that all empyema will respond favorably and under such conditions the empyema must be treated in the usual surgical way. As yet we have not met this exception, but our cases are relatively few in number. We have had one experience with an interlobar empyema which was very difficult to reach with the needle. Cases of this type may always be hard ones to solve, but if one can reach the pus it is possible to treat it by the chemical method of injection. Empyema is not a serious life-endangering problem in the adult, providing it is recognized, but in childhood it is a much more serious affair. As we referred to previously, all the literature that we have been able to locate pertained to the empyema of children, and the results were, according to the authors,

very good. The child's empyema problem may therefore be a favorable field for reinvestigation as also the whole question of pneumonia in young children, which next year is to be studied at the Children's Hospital in Pittsburgh.

Conclusions. 1. Hydroxyethylapocupreine has not produced any visual disturbance in 200 patients who were given large doses of the drug.

2. There has been, especially during the past year, a lowering of the expected mortality. In the positive blood culture group there were 19 recoveries, or 59% mortality, whereas in the non-treated series there were only 4 recoveries, or 85% mortality.

3. The treatment of pneumococcal empyema by the closed method with injections of a 1 or 2% solution of hydroxyethylapocupreine has been effective in a small series of cases.

4. Mixed infection (*II. influenzae* and *Strep. haemolyticus*) has been present to a marked degree during the winter and spring of 1937 in our community.

The authors wish to express their thanks for the assistance during the past year to Drs. M. M. Bracken and George E. Crum. Further studies on the experimental side of this problem will be published.

REFERENCES.

- (1.) Bussel, M., and Hirszfeld, H.: *Rev. franç. d. pédiat.*, 3, 70, 1927. (2.) Dawson, W. T., Permar, H. H., Johnston, J. M., and MacLachlan, W. W. G.: *Am. J. Med. Sci.*, 193, 543, 1937. (3.) Edeiken, J.: *Med. J. and Rec.*, 129, 101, 1929. (4.) Gralka, R.: *Monatschr. f. Kinderh.*, 23, 280, 1922. (5.) Klotz, O.: *Studies on Epidemic Influenza*, Pittsburgh, University of Pittsburgh, p. 207, 1919. (6.) Kolmer, J. A., and Sands, J. R.: *J. Exp. Med.*, 33, 639, 1921. (7.) Leitner, P.: *Monatschr. f. Kinderh.*, 38, 10, 1928. (8.) Lowenburg, H.: *Med. J. and Rec.*, 123, 126, 1928. (9.) MacLachlan, W. W. G., Permar, H. H., Johnston, J. M., and Kenny, J. R.: *Am. J. Med. Sci.*, 188, 623, 1934. (10.) Moore, H. F., and Chesney, A. M.: *Arch. Int. Med.*, 19, 611, 1917; 21, 659, 1918. (11.) Solis-Cohen, S.: *J. Am. Med. Assn.*, 73, 1741, 1919; *Ann. Clin. Med.*, 2, 90, 1923. (12.) Woringer, P.: *Arch. d. méd. des enfants*, 27, 713, 1924; *Rev. franç. d. pédiat.*, 5, 60, 1929.

THE TREATMENT OF ACUTE INFECTIOUS ARTHRITIS OF UNDETERMINED ORIGIN WITH ARTIFICIAL FEVER.*

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THE satisfactory results observed from the treatment of acute gonorrheal arthritis with artificial fever therapy have been fre-

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quently described. Hench *et al.*,⁵ reviewed the reports which appeared since 1932. The results showed cures in from 50 to 100% of the patients treated, with relief in an average of 92%. Other series in which similarly good results were obtained have subsequently been reported by Schnabel *et al.*,¹⁰ Kendell *et al.*,⁶ and Stecher *et al.*¹¹ Little or no attention has been devoted to the efficacy of fever treatment in acute non-specific infectious arthritis and it seems desirable, therefore, to report the results obtained in the following series.

This condition has received scant attention in the literature, though its existence is strongly implied by several authors. Pemberton⁹ does not mention it. Cecil² has no place for it in his classification of arthritis. In discussing the diagnosis of rheumatic fever, however, he says it must be differentiated from "Infectious arthritis, particularly in the subacute or febrile form. . . . In both conditions there is migratory swelling with pain in the joints, and when infectious arthritis is accompanied by fever, the clinical picture presented by these two infections is quite similar. . . . The history of previous attacks will not always settle the question, as the patient may have several attacks of infectious arthritis. However, repeated attacks of infectious arthritis usually will leave some slight deformity, especially in the fingers." Hench⁴ describes many different specific types of acute infectious arthritis, but makes no provision for a similar disease of unknown etiology. Under differential diagnosis, however, he refers several times to "acute infectious (atrophic) arthritis." Such neglect of the subject in the literature is surprising because the disease has been more frequently encountered in this clinic than most of the types described by Hench and Cecil.

As a clinical entity, acute infectious arthritis is characterized by an acute onset of migratory arthritis associated with moderate fever, leukocytosis and rapid sedimentation rate. It is distinguished from gonorrheal arthritis, which it may simulate closely in all other respects, by a negative history and a lack of objective evidence of gonorrhea. Acute infectious arthritis differs from acute rheumatic fever in that it involves one or two joints following the brief migratory onset. Evidence of joint destruction is common. Effusions which have been examined contained neutrophils but were never grossly purulent, while smears and cultures revealed no organisms. In this respect the disease suggests atrophic arthritis. In fact, acute infectious arthritis ultimately may become chronic and assume all the characteristics of atrophic or rheumatoid arthritis.

It is difficult and in some cases impossible at the onset to distinguish between gonorrheal arthritis, acute rheumatic fever and acute non-specific infectious arthritis. All three may manifest fever and leukocytosis and exhibit migratory involvement of numerous joints with pain, tenderness, heat, swelling and effusion. Prompt

subsidence of symptoms with salicylate therapy, the absence of joint damage and the appearance of cardiac murmurs support the diagnosis of rheumatic fever. Evidence of active gonorrheal infection, or a recent history of gonorrhea closely associated in point of time with the appearance of joint symptoms, strongly suggest the diagnosis of gonorrheal arthritis which is, however, never proved until the organisms are recovered from the joint.

The material presented in this paper consists of 20 cases of acute non-specific infectious arthritis. All patients here considered had an unsatisfactory response to salicylate therapy and none developed cardiac murmurs during the period of observation. Only one patient (S. W.) had a previous history of arthritis, an acute attack 3 years before which had produced definite joint changes in an ankle. Six patients developed roentgenographic evidence of joint damage during the present illness. No evidence of gonorrheal infection was discovered. All patients had negative prostatic or cervical smears. Several gave histories of previous gonorrheal infections but none had occurred during the preceding 3 years. The diagnosis of acute rheumatic fever and gonorrheal arthritis seemed to be satisfactorily excluded in these patients.

All but 2 of the patients were in hospital for at least part of their treatments and all have been seen subsequently in the dispensary. In addition to fever therapy they were treated with bed rest and acetylsalicylic acid as indicated. Two patients (A. B. and W. T.) required traction for correction of flexion deformities after the acute symptoms of arthritis had subsided and one (R. B.) had traction followed by a hip spica. One patient (R. S.) required capsulotomy; one (L. C.) had a tonsillectomy; one (E. D.) had aspiration of a knee before fever therapy was instituted; one (D. S.) received 4 injections of typhoid vaccine with good febrile response after cabinet fever therapy had been discontinued.

Apparatus and Procedure. All fever treatments were given with the Kettering Hypertherm, which usually produced a rectal temperature of 105° F. in about an hour. The breeze from an electric fan was directed toward the patient's head, and ice rubbed on his face for comfort. Sodium amytal and morphine were given for sedation, and iced saline to relieve thirst and to replace chlorides lost by sweating. A nurse was in constant attendance. Temperatures of 105° F. to 106° F. were usually employed and were maintained about 5 hours. Occasionally lower temperatures were used and were continued for shorter periods when it seemed advisable to terminate treatments prematurely. Descriptions of the apparatus and procedures^{5,6,10,11} in greater detail have been described repeatedly, particularly in relation to the treatment of gonorrhea.

Results. The most important data are presented in 2 tables, with cases listed in order of increasing duration of arthritic symptoms. The number of fever treatments may be estimated by considering that each treatment lasts from 3 to 5 hours. The actual time spent in the cabinet is much longer, since the period (about

1 hour) required for the temperature rise is not included. Treatments are listed as "hours above 105° F.," although at times the temperature would drop below this level for short periods. In most cases it was maintained continuously above 105° F.

Table 1 shows the data on 12 patients who received complete relief or cure of all joint symptoms. This means that they were free of pain and tenderness; the joints were normal in appearance and were able to perform satisfactorily all the motions required by the patient's usual activity without attracting the attention of an observer. One patient (A. K.) showed incomplete extension and slight enlargement of the metacarpophalangeal joint of a fore-

TABLE 1.—ACUTE NON-SPECIFIC INFECTIOUS ARTHRITIS WITH COMPLETE RECOVERY.

	Sex.	Age.	Duration of arthritis (in weeks)	White blood count on admission.	Sedimentation rate.*	Type of onset.	Major involvement.	Roentgen ray.	Fever hours of 105° F	Comment.
M. B.	F.	21	1	11,100	80	Migratory	Finger	Neg.	8	
J. K.	M.	42	1	10,300	106	Knee, ankle	None	2	
E. D.	M.	48	2	15,000	84	Knee	Neg.	5	Onset with chills. Knee was aspirated.
G. S.	M.	51	2	7,500	108	Migratory	Hands	See note	3	Hypertrophic arthritis of ankle by Roentgen ray.
D. S.	M.	24	2	8,300	110	Knee	Neg.	10	
E. W.	M.	29	2	20,000	90	Migratory	Knee	None	5	Iritis.
E. F.	M.	47	3	9,600	35	Ankle, wrist	Neg.	6	
A. K.	F.	24	3	7,500	127	Migratory	Hand	Erosion	8	Onset after delivery.
C. H.	M.	34	4	12,100	60	Migratory	Hand, elbow	None	6	
F. K.	M.	48	6	16,000	100	Migratory	Wrist, elbow	None	6	
D. S.	F.	39	8	14,000	100	Migratory	Wrist, elbow	None	4	Had 4 injections T. A. B.
J. F.	M.	32	10	9,400	102	Migratory	Wrist, knee	None	25	

* Sedimentation rate by a modified Westergren method. Oxalated but undiluted blood was set up in tubes graduated to 200 mm. and read at the end of 1 hour without correction for anemia. A reading of 20 mm. or less is regarded as normal.

finger 3 months after treatment. This was the only joint involved. A Roentgen ray photograph before treatment showed slight erosion at the edge of the joint, and 3 months later a subsequent film showed mild hypertrophic changes throughout the joint. Roentgen ray photographs were made of the affected joints of 5 other patients of this group. All were normal save one (G. S.), which revealed hypertrophic changes, interpreted as having no significant relationship to the acute infectious arthritis.

Table 2 includes the data on 8 patients who received partial relief. Three of these patients (L. C., S. C., and L. A.) were free of all signs of joint disease after one or two treatments. They had no swelling, tenderness or limitation of motion but they did complain of vague aches and pains which caused them to return to the

dispensary for further relief. Roentgen ray photographs of the affected joints were negative. One patient (S. W.) had a similar result except that the Roentgen ray picture showed erosion at the edge of a metacarpophalangeal joint of a middle finger. A later picture showed mild hypertrophic changes, and he then had incomplete extension. The patient was able to work as a railroad brakeman.

Roentgen ray studies of the affected joints were made on all the patients of this group. In 3 patients (L. C., S. C., and L. A.) these were entirely negative. In 2 cases with joint damage (W. T. and A. B.) one treatment relieved pain and tenderness but marked

TABLE 2.—ACUTE NON-SPECIFIC INFECTIOUS ARTHRITIS WITH PARTIAL RELIEF.

	Sex.	Age.	Duration of arthritis (in weeks)	White blood count on admission.	Sedimentation rate.*	Type of onset.	Major involvement.	Roentgen ray.	Fever hours of 105°F.	Comment.
L. C.	F.	21	2	8,000	115	Migratory	Knees, wrists	Neg.	30	Migratory symptoms without signs for 3 months.
S. W.	M.	30	4	12,000	25	...	Hand	Erosion	20	Migratory symptoms; works as brakeman.
R. B.	F.	14	4	11,800	137	Migratory	Hip	Erosion	12	Lost all motion after using a spica.
S. C.	M.	40	5	13,000	114	Migratory	Knees, wrists	Neg.	22	Migratory symptoms after treatment.
W. T.	M.	40	5	9,150	60	...	Knee	Erosion	15	Required traction for flexion deformity.
A. B.	F.	43	7	8,100	130	Migratory	Knee	Erosion	5	One treatment relieved pain. Required traction for flexion deformity.
R. S.	F.	26	11	7,600	85	Migratory	Knee	Erosion	25	Required capsulotomy.
L. A.	F.	24	16	18,000	113	Migratory	Hands, knees	Neg.	6	Migratory symptoms without signs for 2 months.

* Sedimentation rate by a modified Westergren method. Oxalated but undiluted blood was set up in tubes graduated to 200 mm. and read at the end of 1 hour without correction for anemia. A reading of 20 mm. or less is regarded as normal.

flexion deformity remained. Two subsequent treatments were given to one (W. T.) without improvement of the deformity. Traction in both cases produced correction and the patients have satisfactory joints with painless motion from complete extension to 90 degree flexion. One patient (R. S.) noted substantial but not complete relief of pain and tenderness. Her flexion deformity could not be corrected by traction or casts and a capsulotomy was eventually performed. The remaining patient in this group (R. B.), entered the hospital with a history of severe migratory arthritis of 3 weeks' duration. Examination revealed that all joints had subsided except the right hip which was extremely painful and was held motionless in flexion, abduction and external rotation. Her temperature was high, heart rate rapid, and there was leukocytosis. The provisional diagnosis of rheumatic fever was abandoned after salicylate therapy proved ineffective, and a Roentgen ray picture revealed marked demineralization with destruction of the head of the femur and the upper portion of the acetabulum, suggesting

gonorrheal or tuberculous arthritis. Further study indicated that neither of these infections was present. The first treatment caused definite diminution of pain and reduction of the fever. Two more treatments brought the temperature to normal, eliminated tenderness and relieved spontaneous pain. Traction then corrected the deformity, and the muscle spasm subsided. Motion of the hip at this time was painless and limited from full extension to 60 degrees of flexion with about 30 degrees of internal rotation. Abduction and adduction were slight. Because of marked demineralization of the head of the femur and the acetabulum unprotected weight bearing seemed hazardous and likely to cause deformity of the joint structures. For this reason a walking hip spica was applied before the patient went home. On removal of the spica 6 weeks later the hip was found to be motionless. This lack of motion seemed to be due to hypertrophic changes and bone proliferation about the rim of the acetabulum. The joint space had nearly disappeared but the line of separation between the bones was distinct and there was no evidence of true bony ankylosis.

Two similar cases which occurred in our series of gonorrheal arthritis were given bed exercises for 1 and 2 months until remineralization had taken place and both now have painless movable hips.

Comment. Not only did 60% of the 20 patients make complete, prompt recovery and 40% have partial relief, but the duration of the disease was shortened in all, its severity decreased, the incidence of joint damage lessened and the joint damage which did occur minimized by artificial fever therapy. These results compare favorably with those which have been reported in cases of gonorrheal arthritis treated with fever therapy.

The tables reveal that the 12 patients receiving complete relief had arthritis symptoms from 1 to 10 weeks (average 3.6 weeks), before fever therapy was instituted. These patients received from 2 to 25 hours of fever (105° F.) for relief (average 7.3 hours). The 8 patients having only partial relief had arthritic symptoms from 2 to 16 weeks before fever therapy was instituted (average 6.7 weeks). This group received from 5 to 30 hours of fever (average 17 hours). It is noteworthy also that 5 of the 6 patients showing Roentgen ray evidence of joint damage were of the group of longer duration. These findings indicate the importance of prompt therapy in an effort to avoid or minimize the joint damage. The satisfactory results observed in the first group were obtained with relatively small amounts of fever. Despite the fact that the patients receiving only partial relief had nearly twice as much fever as those in the first group, the authors now feel that several patients suffered from inadequate fever. This is particularly true of one patient (R. B.) who had 3 treatments of 4 hours' duration at weekly intervals. She was treated soon after we started using fever therapy: a period

when conservatism was indicated by inexperience. In an acute disease of short duration there appears to be no reason to delay the second or third treatment more than 3 or 4 days.

The complications of fever therapy encountered in this series were neither as frequent nor as severe as those seen in our series of gonorrheal arthritis.¹¹ Because the degree of fever desired and attained was more moderate, 105° F. in this series as compared with 107° F. or higher in the other, the air temperature of the cabinet was maintained at a consistently lower level, discomfort of the patient was less severe, and delirium was rare, while coma, collapse and uncontrolled hyperpyrexia were not seen. Sedation was less difficult, and smaller doses of sodium amytal and morphine were necessary than in treating gonorrhea. Consequently, delirium from sodium amytal and nausea from morphine, which proved a troublesome problem in many patients treated at higher temperatures, rarely occurred in this series, and severe erythemata and skin burns usually were avoided. One treatment was terminated after 4 hours because of blisters. This patient (D. S.) subsequently developed second degree burns which made further fever treatment inadvisable at the time. One complication, the occurrence of herpes labialis, developed as frequently in the present series as it did in the series treated at the higher temperature. About one-third of the patients in each series developed herpes labialis but it occurred only after the first treatment.

Discussion. Although the treatment of acute infectious arthritis with artificial fever must be regarded as empirical, its use is not without precedent. Protein shock therapy,^{3,9} such as boiled milk injections or typhoid vaccine intravenously, has been used with some success in various types of arthritis for years and still enjoys popularity. Similar therapy for chorea and rheumatic fever¹² is highly recommended, and the authors of recent reports⁸ are enthusiastic in praise of mechanical fever for chorea. The causes of acute rheumatic fever, chorea and atrophic arthritis have not thus far been indisputably demonstrated, but there is much evidence to indicate that streptococci are concerned in all three, together with other factors not clearly understood.

There has been no adequate explanation for the beneficial effects of fever therapy in acute infectious arthritis. The mechanism is not clear. In such a disease of unknown etiology there is no justification for assuming that high temperatures directly produce death or destruction by thermal injury to the causative agent. In only two diseases, gonorrhea¹ and syphilis,² has it been established that this may occur. Patients with these diseases can tolerate temperatures of sufficient height and duration to sterilize *in vitro* cultures of the causative organisms. Thermal death time studies of cultures of many other pathogenic organisms show them to be more tolerant

of high temperatures than is man.⁷ The streptococci are among this group of more thermostable organisms.

Definite physiological changes are produced by artificial fever.⁵ The blood flow, circulatory rate, cardiac output and metabolism are increased. An increase in the number and size of capillaries has been observed to occur in the nail bed, and the drop in diastolic blood pressure and the rise in the pulse-pressure indicates that this change is general throughout the body. The leukocyte count, after an initial fall, shows a substantial rise and the rate of phagocytosis increases. Reports on agglutinins, complement and opsonic index are variable. It seems probable that the beneficial effects of artificial fever depend upon factors which are not entirely recognized.

Summary. Acute non-specific* infectious arthritis is a relatively common syndrome which may be differentiated from acute rheumatic fever and acute gonorrheal arthritis by certain well defined distinguishing characteristics. It has received scant attention in the literature and may be regarded as an acute form of atrophic, rheumatoid or chronic infectious arthritis. Of the 20 cases of acute non-specific infectious arthritis treated with artificial fever therapy, 12 (60%) received prompt relief and apparent cure, while 8 (40%) were partially relieved. The course of the disease was favorably modified in every case. These results compare favorably with those observed in the treatment of acute gonorrheal arthritis by artificial fever.

Treatment consisted of induced fever (about 105° F.) by means of the Kettering Hypertherm, maintained usually from 4 to 5 hours. The patients who recovered completely received from 2 to 25 hours of fever (average 7.33 hours). The patients with partial relief received 5 to 30 hours of fever (average 17 hours).

The use of artificial fever in this condition is empirical but not without precedent. The mechanism producing benefit is not understood.

* By non-specific is meant a process that is obviously infectious and yet has not had the causative organism or organisms identified.

REFERENCES.

- (1.) Boak, R. A., Carpenter, C. M., and Warren, S. L.: The Thermal Death Time of 130 Strains of *Neisseria Gonorrhoea*, Abst. Papers and Discussions, Fifth Annual Fever Conf., Dayton, Ohio. May 2 and 3, 1935.
- (2.) Cecil, R. L.: The Diagnosis and Treatment of Arthritis, Oxford Monographs, New York, Oxford Univ. Press, 7, 15, 1929.
- (3.) Epstein, N. N., and Cohen, M.: J. Am. Med. Assn., 104, 883, 1935.
- (4.) Hench, P. S.: Acute and Chronic Arthritis, Nelson Loose-Leaf Surgery, 3, 113, 1935, New York, Thomas Nelson & Sons.
- (5.) Hench, P. S., Slocumb, C. H., and Popp, W. C.: J. Am. Med. Assn., 104, 1779, 1935.
- (6.) Kendell, H. W., Webb, W. W., and Simpson, W. M.: Am. J. Surg., 29, 428, 1935.
- (7.) Krusen, F. H.: J. Am. Med. Assn., 107, 1215, 1936.
- (8.) Neymann, C. A., Blatt, M. L., and Osborne, S. L.: Ibid., p. 938.
- (9.) Pemberton, R.: Arthritis and Rheumatoid Conditions, Philadelphia, Lea & Febiger, 1929.
- (10.) Schnabel, T. G., and Fetter, F.: Ann. Int. Med., 9, 398, 1935.
- (11.) Stecher, R. M., and Solomon, W. M.: Am. J. Med. Sci., 192, 497, 1936.
- (12.) Sutton, L. P., and Dodge, K.: J. Pediat., 3, 813, 1933.

EXPERIMENTAL STUDIES ON THE EFFECT OF TEMPORARY OCCLUSION OF CORONARY ARTERIES IN PRODUCING PERSISTENT ELECTROCARDIOGRAPHIC CHANGES.*

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ACCORDING to current belief, both angina pectoris and cardiac infarction are the result of myocardial ischemia. In each the underlying mechanism seems to be a relative disproportion between the requirements of the heart for blood and the supply furnished by the coronary arteries; the changes resulting from this situation depend solely upon the extent and duration of the relative ischemia of the myocardium, however it may be produced. Thus, the syndrome of Heberden's angina pectoris is due to temporary ischemia, while the manifestations of coronary occlusion are the result of a permanent ischemia, with infarction of the muscle supplied by the occluded vessels. In patients with clinical evidence of coronary occlusion, infarcted areas of the cardiac musculature are not infrequently disclosed at postmortem examinations even though the arteries supplying the area, while they may be narrowed, are not completely occluded. Similarly, many patients with angina pectoris show persistent electrocardiographic abnormalities during life, and at postmortem examinations present small areas of cardiac fibrosis despite the absence of occluded arteries. It would thus appear that temporary ischemia may result in certain irreversible electrocardiographic and anatomic changes. The situation is analogous to that occurring in carbon monoxide poisoning where, despite restitution of normal blood oxygen, severe neurologic disturbances occur because the temporary ischemia has been sufficient to produce irreversible changes in the brain which lead to necrosis.

In an experimental investigation of the reaction of the myocardium to temporary ischemia, the following manifestations of deficient myocardial nutrition may be considered: 1. Disturbances of the

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myocardial metabolism; 2, changes in cardiac rhythmicity and contractility; 3, alterations in the ventricular electrocardiographic complexes; 4, necrosis of myocardial fibers.

These changes and their degree indicate the existence of impaired myocardial nutrition and serve as an index of its severity. In man, they are reflected in the signs and symptoms of coronary disease.

The Arrhythmias of Cardiac Ischemia. Erichsen,⁸ in 1842, reported "tremulation of the ventricles" within 30 seconds to 2 minutes following ligation near the origin of main coronary arteries in rabbits and in dogs. Subsequently, many other investigators observed slowing, irregularities of rhythm, and finally ventricular fibrillation after sudden occlusion of one or more main coronary trunks in rabbits, dogs and cats.^{1a,b,3, 6, 7,13,16-18,23,26,31} In many instances the appearance of ventricular fibrillation was observed within a few seconds after occlusion, while at other times ligation of the same artery resulted either in no fibrillation or in fibrillation some hours after occlusion. Sudden release of the ligature occluding a main artery or one of its branches has been observed to initiate extrasystoles and ventricular fibrillation within a few seconds.^{7,10}

Ligation of lesser branches of the main coronary arteries produced ventricular fibrillation much less frequently. Continuance of normal auricular contraction despite the arrhythmia of the ventricles has been described.²⁶

From these and other reports it appears that the following factors may exert an important influence in precipitating ventricular fibrillation: 1, size of artery occluded; 2, region of heart supplied by the artery occluded;¹² 3, duration of occlusion; 4, nature of the anesthesia;¹⁴ 5, activity of autonomic nervous system;^{13b,27} 6, changes consequent to reestablishment of circulation.

The Dynamics of the Heart in Coronary Occlusion. The decreased force of myocardial contraction consequent to coronary ligation was observed by Erichsen,⁸ von Bezold^{1a,b} and other early experimentors, and has been recognized by all subsequent workers. It remained, however, for Tennant and Wiggers²⁸ to devise a method for optical registration of the contraction of portions of myocardium *in situ*, and to show that the force of contraction fails within a minute after occlusion of the coronary artery supplying the region studied. They found that when circulation was reestablished after 20 minutes or less the myocardial contractility returned to normal, while with longer occlusion recovery did not take place. Their experiments were, however, acute and it is not known whether recovery might have occurred several hours or days later.

The Electrocardiogram in Coronary Occlusion. Changes in the electrical behavior of heart muscle following coronary occlusion were first described by Samuelson in 1880.²⁵ Using the rheoscopic frog preparation as an index of electrical activity in the heart, he found that when a coronary artery was occluded in a curarized

rabbit, the frog muscle ceased to contract as soon as the effects of the occlusion could clearly be recognized by change in color of the ventricle and alterations in rhythm. Within $\frac{1}{2}$ to $1\frac{1}{2}$ minutes after release of the ligature, contractions of the rheoscopic preparation returned to normal. This experiment could be repeated many times in the same animal with the identical results. It has since been recognized that characteristic alterations of the ventricular electrocardiogram may develop very shortly after coronary occlusion, both in man and in experimental animals. Otto,²¹ Parade,²² Wood and Wolferth,^{31b} Wilson, Hill and Johnston,³⁰ Garcia del Rio and Orias,⁹ and others have detected these changes within 1 to 10 minutes after experimental coronary occlusion. Several of these authors^{11,31a} have also shown, as did Samuelson, that if the circulation is reestablished after but 1 to 3 minutes of occlusion, the electrical activity of the ventricles returns promptly to normal. Determinations have not been made of the time of occlusion necessary to produce permanent or long lasting electrocardiographic changes.

Myocardial Necrosis. It has long been recognized that infarcts in the myocardium may result from occlusion of coronary arteries, and the investigations of Büchner^{4a,b,c} and others^{5,19} have demonstrated that prolonged cardiac anoxemia from other causes may also cause necrosis. Temporary occlusion for 2 hours or more, when followed by reestablishment of circulation, has been found to lead to necrosis of the myocardium supplied by the occluded vessel, while occlusion for 30 minutes was not followed by necrosis.^{10,24,29}

It is evident from this survey of available knowledge that adequate data are lacking concerning the following questions:

1. May temporary interruption of the blood supply to a part of the heart produce persistent electrocardiographic changes?
2. If this proves to be the case, how long must such temporary ischemia be maintained in order to produce persistent electrocardiographic changes?
3. What is the relation between the duration of coronary circulatory arrest causing electrocardiographic changes and the duration of arrest required to produce myocardial necrosis?
4. What effect has the duration of temporary circulatory arrest upon the development of cardiac irregularities during the arrest and after reestablishment of a normal blood supply?

The present studies were designed to gain evidence in regard to these considerations.

Methods. In 24 cats the anterior descending branch of the left coronary artery or one of its larger ramifications was occluded for varying lengths of time.

With the animal under ether anesthesia and artificial respiration, the heart was exposed through an intercostal approach. The pericardium was opened; the artery to be occluded was dissected free from the adjacent tissue over a length sufficient to allow a silk or catgut ligature to be placed

loosely beneath it. The accompanying vein was never included in the ligature. At the appropriate time gentle traction was exerted on the ligature to the point of complete occlusion of the artery, and subsequently released after periods of traction varying from 5 to 40 minutes. The ligature was then removed, the pericardium sutured, and the chest closed. Fifty cc. of 5% glucose in physiologic saline was given intraperitoneally and the animal placed in a warm room.

Electrocardiographic tracings from Leads 1, 2 and 3 were taken with the ligature in place just before traction was begun. In each animal a continuous tracing was taken from Lead 2, starting just before traction was exerted, and running for approximately 1 minute after the beginning of traction. Records were taken from Lead 2 or all three leads at intervals of 2 to 10 minutes during traction. Lead 2 tracing was again started just before release of traction and continued until approximately 1 minute after release. Electrocardiographic tracings from all three leads were repeated at intervals, up to 30 minutes after release of traction, and at 1 to 2-day intervals until the animal was sacrificed.

The cardiac musculature was observed carefully for changes in contraction and color before, during and immediately after traction. Inspection of the freed coronary vessel distal to the point of traction demonstrated its complete obstruction during traction, and the reestablishment of blood flow upon release. The animals were sacrificed 6 to 9 days after operation. At this time the heart was again exposed under ether anesthesia and artificial respiration, and observations were made of the appearance of the myocardium and of the vessel which had been temporarily occluded; the patency of this vessel was demonstrated by observation of bleeding after incision below the point of previous ligation.

The heart was then removed, examined for gross changes in the myocardium, and fixed in 5% solution of formaldehyde. Cross sections of the heart were made at various levels above and below the point of occlusion and were studied to determine changes in the myocardium and in the coronary vessels. Sections of the coronary artery at the region of the tie demonstrated the absence of traumatic changes or thrombus formation.

Control observations were made on 6 cats. In 4, the ligature was put in place and then removed without occluding the vessel; the animals were allowed to survive and electrocardiographic tracings were made in 3 on the day after operation; in the fourth, at intervals during the week following operation. At the time of sacrifice, anatomical studies of the heart were made in each animal. In the other 2 control experiments the ligature was permanently tied; electrocardiographic tracings were obtained at intervals during the postoperative week and anatomical studies were made.

Results. A. *Electrocardiographic Changes.* Electrocardiographic changes following temporary coronary artery occlusion are summarized in Table 1. In all but 2 of the cats studied, tracings showed the development of definite anoxic changes within 1 minute after traction was applied; in the other 2 cats definite changes were first evidenced at 2 and 15 minutes after the beginning of traction. These changes became more pronounced during the time of occlusion, and, while they generally persisted immediately after release of the ligature, they were somewhat less pronounced (Table 1). They consisted in definite alteration in the *R* or *S-T* take-off elevated or depressed *S-T* segments and marked changes in the *T* waves (Figs. 1, 2 and 3). Changes in the direction of the *QRS* complexes were occasionally witnessed, but evidences of intraventricular block were not seen.

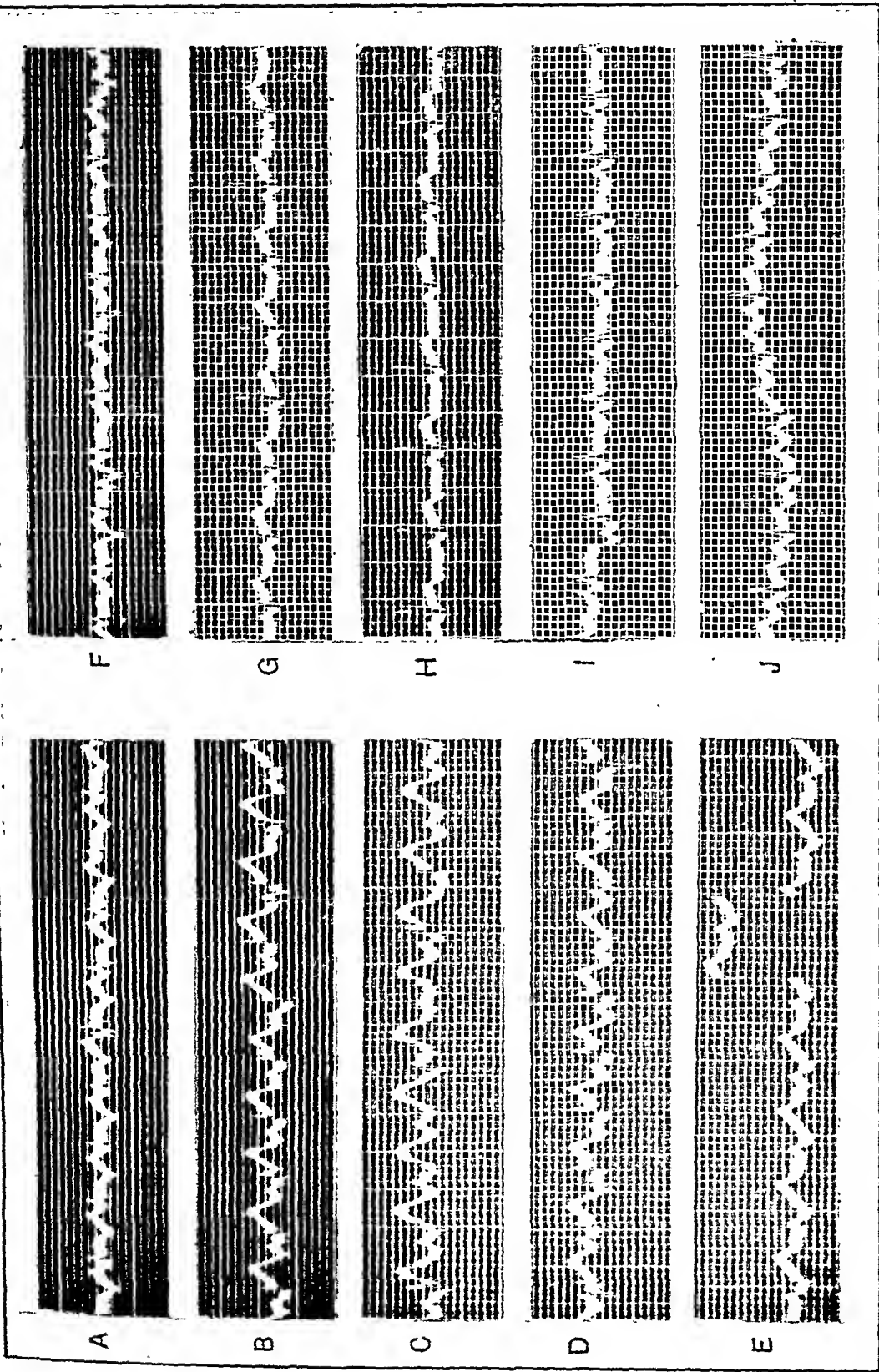


FIG. 1.—Cat 3. Occlusion of left anterior descending artery for 10 minutes. Lead 2 throughout. A, Control; immediately before traction; B, after 1 minute of traction; C, after 4 minutes; D, after 10 minutes; immediately before release; E, 11 minutes (1 minute after release); F, first postoperative day; G, second postoperative day; H, sixth postoperative day; I, seventh postoperative day; J, eighth postoperative day.

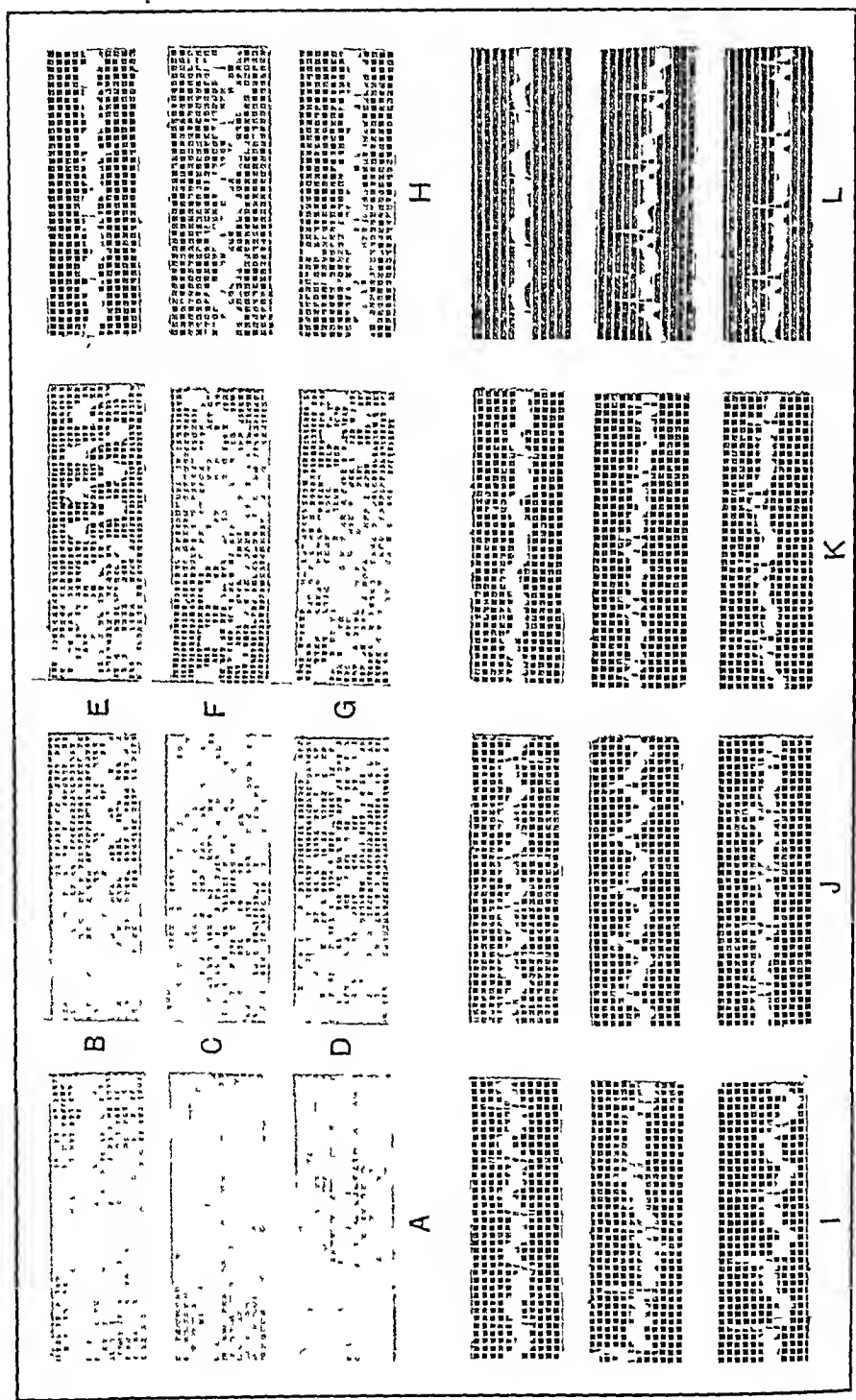


Fig. 2.—Cat 2. Occlusion of left anterior descending artery for 10 minutes. Electrocardiograms by the conventional three leads were of the inferior infarction type. A, Control (three leads); B, 10 seconds after traction (Lead 2); C, 20 seconds (Lead 2); D, 1 minute (Lead 2); E, 3 minutes (Lead 2); F, 9 minutes (Lead 2); G, 10 minutes (Lead 2); H, three leads in this and following columns, first post-operative day; I, third post-operative day; J, fourth post-operative day; K, sixth post-operative day; L, seventh post-operative day.

These electrocardiographic changes persisted during the entire postoperative period in all cats in which the period of occlusion was 15 minutes or longer. Persistent electrocardiographic changes were observed, however, in only 3 of the 6 experiments in which traction was exerted for 10 minutes or less. One of these 3 animals showed changes until sacrificed 8 days postoperatively. The changes during

TABLE 1.—ELECTROCARDIOGRAPHIC CHANGES FOLLOWING TEMPORARY CORONARY ARTERY OCCLUSION IN CATS.

Cat No.	Date (1936).	Duration of occlusion (min.).	Degree of electrocardiographic abnormalities.		Postoperative electrocardiographic abnormalities.		Sacrifice of animal, days post-operative.
			During occlusion.	Immediately after occlusion.	Duration (days).	Degrec.	
1	6/3	5	++	2	+++	8
2	5/27	6	+	0	0	7
3	6/3	10	+++	+	8	++	8
4	4/24	10*	+++	V.F.	0	0	6
5	5/25	10	++	+	0	0	9
6	4/17	10	+++	+	3	+	7
7	4/22	15	7	++	7
8	4/17	15	7	+++	7
9	4/24	15	+++	++	6	+++	6
10	5/18	20	+++	++	1§
11	5/10	20	+++	++	7	++	7
12	5/13	20	+	+	6	+	6
13	4/21	20	+	7	+	7
14	4/22	20	+++	0	2	+	2§
15	5/11	25	+++	+	1	++	1§
16	5/8	30	+++	0	7	++	7
17	5/8	30	+++	+	7	+++	7
18	5/8	30	+++	+	3	++	8§
19	5/13	30	+	+	6	+	6
20	5/11	35	+++	++	7	++	7
21	5/11	40*	+++	V.F.	1§
22	6/3	3†	++	V.F.	0§
23	5/8	30†	++	V.F.	0§
24	5/13	30†	V.F.	0§

* Fibrillated on release of ligature. Recovery.

† Fibrillated during occlusion. Death.

‡ Fibrillated on release of ligature. Death.

V.F.=Ventricular fibrillation.

|| Last electrocardiograph taken.

§ Animal died.

the postoperative period varied somewhat from day to day, but generally were qualitatively similar to those witnessed during occlusion. In almost all instances the electrocardiographic changes were those characteristic of anterior infarction and corresponded closely to the deviations produced by permanent ligature of the same artery in two controls.

In 3 of the 4 experiments in which the ligature was put in place

and then withdrawn without traction, electrocardiographic records taken before and after the procedure were practically identical. In the fourth experiment, minimal changes were noticed in Lead 2

Cat 9, 15 Minute Occlusion L. A. D.

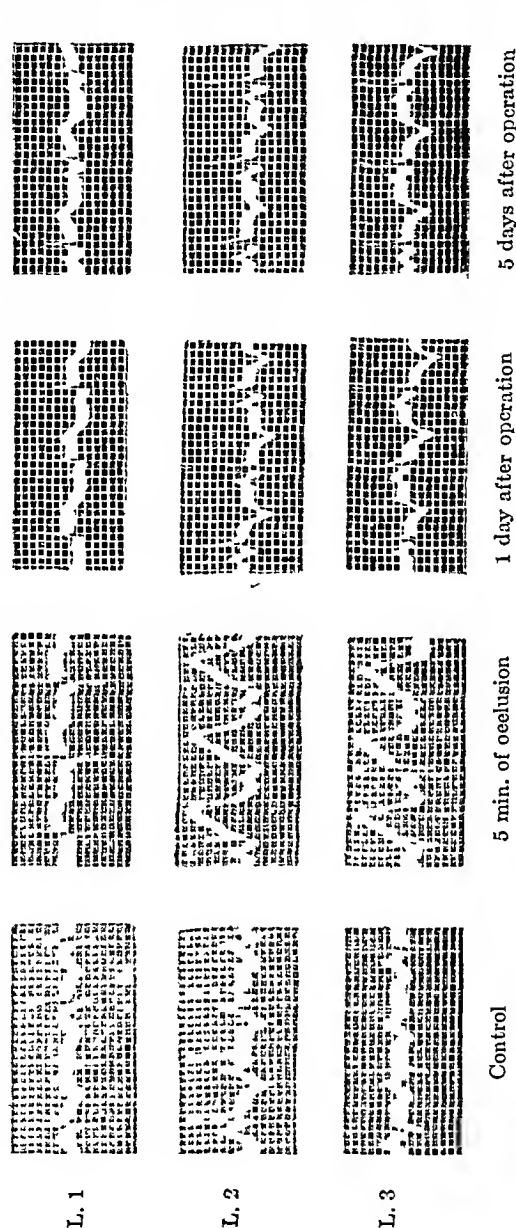


Fig. 3.—Cat 9. Occlusion of left anterior descending artery for 15 minutes, showing electrocardiograms of conventional three leads just before occlusion of the artery, 5 minutes after the beginning of occlusion, and 1 and 5 days after the operation.

but were insignificant in comparison to the results following temporary occlusion. These findings, together with the absence of electrocardiographic changes postoperatively in 3 of the 6 animals

in which occlusion was maintained for 10 minutes or less, constitute important evidence that other factors such as pericarditis or local thrombosis were not significant in producing the electrocardiographic changes observed in this study.

B. Changes in the Myocardium. Within a few seconds after application of traction on the artery, the myocardial area supplied became cyanotic and showed diminished contraction. These changes became more pronounced during the period of traction; when the ligature was released the affected portion of the myocardium resumed its normal color.

On sacrificing the animals no gross or histologic evidences could be found which might be interpreted as due to the temporary occlusion. Minute areas of focal necrosis were found histologically, but similar areas were also seen in unaffected areas of these hearts and in the hearts of a large series of normal cats. Permanent ligation of the same arteries in 2 control cats resulted in definite infarcts.

C. Arrhythmias. Soon after the onset of traction isolated ventricular extrasystoles were frequently encountered, which, with but one exception, did not proceed to paroxysmal ventricular tachycardia or to ventricular fibrillation during occlusion. Shortly after release of traction, however, 4 of the 24 animals rapidly developed ventricular fibrillation, from which 2 died.

Discussion. In the light of these findings it appears that temporary cardiac ischemia may result in lasting electrocardiographic changes, in the absence of any discernible histologic evidence of myocardial necrosis. In all of the 13 animals in which occlusion of the anterior descending branch of the left coronary artery or one of its main branches was for 15 minutes or longer, significant deviations from normal persisted postoperatively until the animal was sacrificed on the sixth to ninth postoperative days. The changes consisted in: 1, elevation or depression of the *S-T* take-off; 2, loss of the iso-electric *S-T* segment; and, 3, alteration in the direction, amplitude and contour of the *T* wave. These findings corresponded in every way with those following permanent occlusion of the same vessel in control experiments, and conform to those described as characteristic of infarction of regions of the anterior wall of the ventricles.

In all except 2 animals the first appearance of electrocardiographic changes was observed within 1 minute after occlusion of the vessel, and became more pronounced as occlusion continued. Immediately after release, these changes decreased somewhat in degree, and in 2 experiments an almost normal electrocardiogram was reestablished. By the first postoperative day, however, these changes again became more pronounced, and then showed a tendency to gradual subsidence.

When occlusion was maintained for less than 15 minutes the changes in the electrocardiogram during the period of arrest of

coronary flow were as well pronounced as when the duration of occlusion was longer. In 3 of 6 such experiments, changes persisted for several days; in the others, significant alterations were not observed postoperatively. Of the 3 positive experiments, 2 showed changes only as long as the second and third postoperative days, while the other, in which the artery was occluded for 10 minutes, showed changes until sacrificed on the eighth day. No similar changes were found in 4 control experiments in which the entire operation was duplicated, with the sole exception of traction on the ligature.

Careful gross and microscopic examination of the hearts failed to reveal any areas of myocardial necrosis that could be attributed to the occlusion. They further demonstrated the absence of thrombi or other occlusion in the artery at the point of temporary occlusion or peripheral to it. The reestablishment of normal blood supply following release of traction on the artery was verified by certain other observations: 1, following release of the ligature, the area supplied by the artery, which had been clearly demarcated by its cyanotic and edematous appearance, immediately resumed its normal color; 2, pulsation of the artery distal to the occlusion was immediately reestablished and its lumen became filled with bright red blood; 3, at the time of sacrifice transection of the artery distal to the tie was followed by arterial spurts of blood. The absence of necrosis likewise indicates that permanent occlusion did not occur.

The unexpected production of long-lasting electrocardiographic changes without tissue necrosis raises interesting questions regarding the interpretation of the electrocardiogram in coronary disease. It is, of course, recognized that, experimentally, short periods of coronary insufficiency are followed by a rapid restoration of the altered electrocardiogram,^{31a} while, on the contrary, sustained ischemia following permanent coronary artery ligation produces persistent electrical disturbances as well as anatomical lesions. It would seem that the observations recorded here fit into an intermediate zone between these two extremes, where myocardial damage has been just insufficient to cause gross tissue destruction, yet functional impairment was so profound that electrical recovery was not complete for periods as long as 9 days. It is not improbable that examination of the affected tissue by special techniques would reveal changes in its staining reactions and in its metabolism.

Counterparts of the conditions revealed in these experiments are seen in patients with angina pectoris. During attacks of angina pectoris, electrocardiograms characteristic of myocardial ischemia which revert to normal at the end of the seizure have been frequently obtained. Many patients with angina pectoris show persistent electrocardiographic abnormalities without postmortem evidence of coronary occlusion or myocardial infarction; the pathologic physiology that occurs in such cases appears to be similar to that of above experiments.

The circumstances under which ventricular fibrillation occurred in these experiments supports the view that this arrhythmia may occur in the absence of irreparable structural damage, for the duration of occlusion of these experiments was insufficient to produce signs of cardiac necrosis. The frequent occurrence of ventricular fibrillation in these experiments is in accord with the view that sudden death in angina pectoris is due to the onset of this arrhythmia. It is not surprising, therefore, that Levy and Bruenn¹⁵ were unable to discover any pathologic explanation for the sudden death of several of the patients in their series.

It is significant that in practically every instance the onset of fibrillation occurred upon release of the ligature and reestablishment of a normal blood supply to the damaged area. The development of ventricular extrasystoles soon after occlusion of the artery, although they did not proceed to ventricular fibrillation, and the frequent reports in the literature of rapid development of ventricular fibrillation soon after occlusion, suggests that the period of transition from normal to abnormal metabolism or *vice versa*, is the most favorable time for development of fibrillation. This view is emphasized by de Boer^{2a,b} who pointed out that it is impossible for completely functionless myocardial tissue to give rise to ectopic rhythms. It is also in accord with the concept that ventricular fibrillation is not necessarily a manifestation of irreparable damage to the heart. This view is further supported by the observation that, clinically, ventricular fibrillation may occur in a variety of other circumstances: 1, the early stages of chloroform anesthesia; 2, acute benzol poisoning; 3, electric shock with low voltages; 4, following intravenous administration of adrenalin; 5, as a termination of paroxysmal ventricular tachycardia, in all of which conditions structural damage is not characteristically present. The occurrence of ventricular fibrillation in cardiac infarction and in other situations in which the heart is irreparably damaged may be due to the presence of zones of impaired nutrition in proximity to areas of complete ischemia.

Summary and Conclusions. 1. Since according to current belief angina pectoris and cardiac infarction are the result of myocardial ischemia, experiments were undertaken to learn whether temporary interruption of the blood supply to a portion of the heart would result in persistent electrocardiographic or anatomic changes.

2. Occlusion of the left anterior descending coronary artery or one of its branches for from 5 to 40 minutes with subsequent release of traction was performed in 24 cats. Twenty-one animals were allowed to survive for from 1 to 9 days after this procedure.

3. Electrocardiograms of the three conventional leads obtained before and at various intervals during and following occlusion revealed anoxic changes persisting during the postoperative days in all animals in which occlusion was maintained for from 15 to 40 minutes inclusive. Only 3 of 6 animals in which the period of

occlusion was 10 minutes or less showed changes on the postoperative days; in one these changes persisted until sacrifice of the animal 8 days postoperatively. The electrocardiographic changes were characteristic of the anterior infarction type.

4. Postmortem examination failed to reveal gross or histologic evidences of cardiac infarction in any instance.

5. Cardiac irregularities consisting of ventricular extrasystoles and ventricular fibrillation were observed at times during occlusion but particularly on release of traction. Three of the 5 animals which developed ventricular fibrillation died immediately.

6. The clinical counterparts of these experimental observations are discussed.

REFERENCES.

- (1.) v. Bezold, A.: (a) *Untersuch. a. d. physiol. Lab. in Würzb.*, 1, 256, 1867; (b) *Centralbl. f. d. med. Wissensch.*, 5, 353, 1867. (2.) de Boer, S.: (a) *Ergebn. d. Physiol.*, 21, 1, 1923; (b) *Deutsch. Arch. f. klin. Med.*, 143, 20, 1923. (3.) Braun Menendez, E., and Orias, O.: *Compt. rend. Soc. de biol.*, 116, 445, 1934. (4.) Buchner, F.: (a) *Beitr. z. path. Anat. u. z. allg. Path.*, 89, 644, 1932; (b) *Klin. Wehnschr.*, 11, 1737, 1932; (c) *Beitr. z. path. Anat. u. z. allg. Path.*, 92, 311, 1933. (5.) Christ, C.: *Beitr. z. path. Anat. u. z. allg. Path.*, 94, 111, 1934. (6.) Coelho, E., and Rocheta, J.: *Compt. rend. Soc. de biol.*, 102, 203, 1929. (7.) Cohnheim, J., and von Schulthess-Rechberg, A.: *Arch. f. path. Anat.*, etc., 85, 503, 1881. (8.) Erichsen, J. E.: *London Med. Gaz.*, 30, 561, 1842. (9.) Garcia del Rio, J., and Orias, O.: *Compt. rend. Soc. de biol.*, 117, 461, 1934. (10.) Harris, B. R., and Hussey, R.: *Am. Heart J.*, 12, 724, 1936. (11.) Hill, I. G. W.: *J. Physiol.*, 81, 70, 1934. (12.) Kronecker, H.: *Ztschr. f. Biol.*, 34, 529, 1896. (13.) Leriche, R., Herrmann, L., and Fontaine, R.: (a) *Compt. rend. Soc. de biol.*, 107, 545, 1931; (b) *Ibid.*, p. 547. (14.) Levy, A. G.: *Heart*, 5, 299, 1913-14. (15.) Levy, R. L., and Bruenn, H. G.: *J. Am. Med. Assn.*, 106, 1080, 1936. (16.) Lewis, T.: *Heart*, 1, 98, 1909. (17.) Michaelis, M.: *Ztschr. f. klin. Med.*, 24, 270, 1894. (18.) Miller, J. L., and Matthews, S. A.: *Arch. Int. Med.*, 3, 476, 1909. (19.) Opitz, v. E.: *Ztschr. f. Kreislaufforsch.*, 27, 227, 1935. (20.) Orias, O.: *Am. J. Physiol.*, 100, 629, 1932. (21.) Otto, H. L.: *Am. Heart J.*, 4, 346, 1928. (22.) Parade, G. W.: *Arch. f. exper. Path. u. Pharmacol.*, 163, 243, 1931. (23.) Porter, W. T.: *J. Physiol.*, 15, 121, 1893. (24.) Ramsey, E. M., Gaiser, D. W., Carden, G. A., Jr., LeCompte, P. M. et al.: *Yale J. Biol. and Med.*, 9, 13, 1936. (25.) Samuelson, B.: *Centralbl. f. d. med. Wissensch.*, 18, 209, 1880. (26.) See, G., Bochefontaine and Roussy: *Compt. rend. Acad. d. sci.*, 92, 86, 1881. (27.) Sutton, D. C., and King, W. W.: *Proc. Soc. Exp. Biol. and Med.*, 25, 842, 1928. (28.) Tennant, R., and Wiggers, C. J.: *Am. J. Physiol.*, 112, 351, 1935. (29.) Tennant, R., Grayzel, D. M., Sutherland, F. A., and Stringer, S. W.: *Am. Heart J.*, 12, 168, 1936. (30.) Wilson, F. N., Hill, I. G. W., and Johnston, F. D.: *Ibid.*, 9, 596, 1934. (31.) Wood, F. C., and Wolferth, C. C.: (a) *Arch. Int. Med.*, 47, 339, 1931; (b) *Ibid.*, 51, 771, 1933.

PULMONARY CIRCULATION IN ARTIFICIAL PNEUMOTHORAX AND ANTHRACOSILICOSIS.

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POSTMORTEM examination¹ of 18 tuberculous lungs which had been collapsed under artificial pneumothorax for a period varying from 5 months to 3 years showed a marked shortening and narrowing



FIG. 1.—Case 6668, white female, aged 20, had pulmonary tuberculosis since August, 1935. The right lung was collapsed under artificial pneumothorax from June to November, 1936. Died in November, 1936. The right pulmonary artery and its branches are shorter and narrower than those in the left lung.

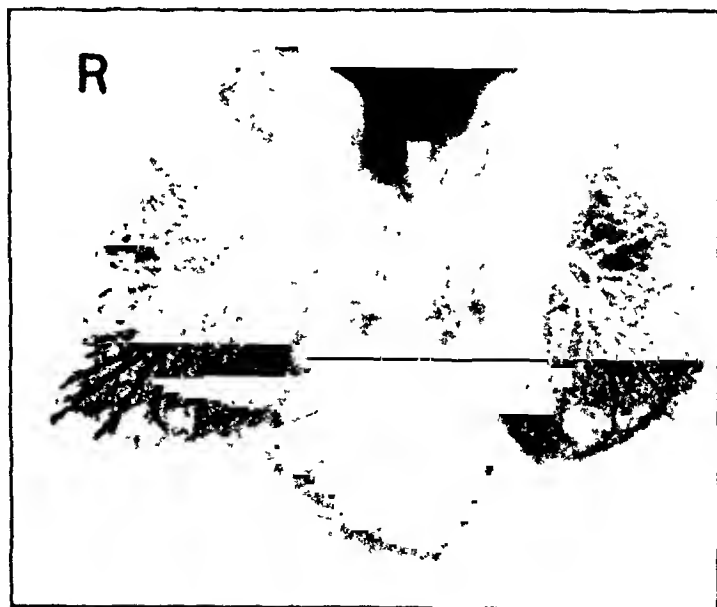


FIG. 2.—Case 6511, white female, aged 24, had pulmonary tuberculosis since January, 1933. The left lung was collapsed under artificial pneumothorax from August, 1934, to August, 1935. Phrenicectomy was done on the left in December, 1935. The left half of the diaphragm became elevated. Died in February, 1937. Note the marked narrowing and shortening of the pulmonary artery and its branches in the left lung.



FIG. 3.—Case 9768, white male, aged 41, anthracite coal miner 16 years. The upper lobes are fibrotic and the lower lobes emphysematous. The pulmonary artery in each lung is shortened and its branches in the upper lobes are destroyed. In the lower lobes the vessels are narrowed due to emphysema.

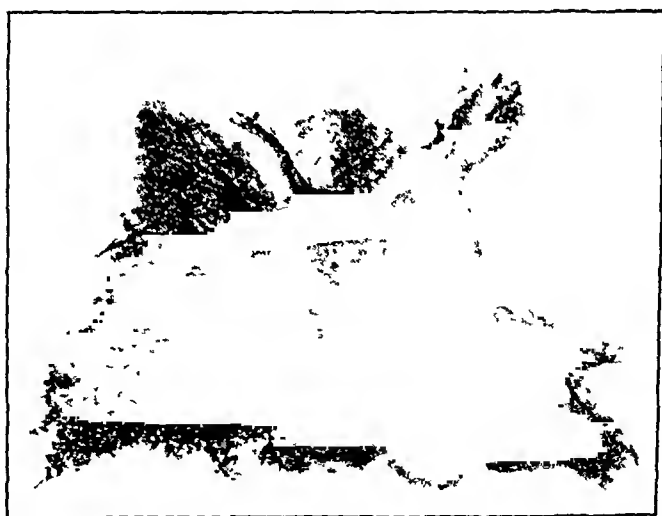


FIG. 4.—Case 9585, white male, aged 45, anthracite coal miner 26 years. The left lung has a large tuberculous cavity. The left lower lobe is fibrotic. Note the marked narrowing of the pulmonary artery near the cavity in the left lung.

of the pulmonary vessels due to sclerosis (Figs. 1 and 2). Somewhat similar sclerotic changes occur in the vessels of anthracosilicotic lungs due to the irritation of the coal and silica and due to intrapulmonary hypertension accompanying emphysema which almost always coexists with anthracosilicosis. We see in addition to sclerosis of the vessels diminution in number of the vessels in excavated areas (Figs. 3 and 4). In presence of such vascular changes the alterations, if any, that may occur in the pulmonary circulation present an interesting problem.

The present communication reports observations on the pulmonary circulation in 20 cases of unilateral pulmonary tuberculosis treated with artificial pneumothorax, 15 cases of pure anthracosilicosis and 10 cases of anthracosilicosis in association with pulmonary tuberculosis.

Method. The pulmonary circulation time devised by Winternitz, Deutsch and Brull,³ using the bitter tasting property of sodium dehydrocholate, was employed with slight modification. Having rinsed the mouth the patient rested on the back for 5 minutes with the right arm raised to the level of his heart. Using a 19-gauge needle attached to a 5 cc. Luer syringe, 2 cc. of 20% sodium dehydrocholate was injected into the antecubital vein, taking not more than 2 seconds. The patient was instructed to signify the instant he noticed a bitter taste on his tongue. The interval between the injection and the bitter taste was taken as the pulmonary circulation time. Ten to 12 seconds as found in a group of normal adults was used as the normal standard time.

Results and Discussion. In the artificial pneumothorax group the pulmonary circulation time varied from 7 to 13 seconds, in the pure anthracosilicotic group 12 to 30 seconds and in the tuberculous anthracosilicotic group 11 to 60 seconds.

The Roentgen ray films of the lungs of these three groups of cases compared with the films of those which came to necropsy show no remarkable difference. From this we presume that the same vascular changes are present in the living as in the necropsied lungs. It is interesting, then, to note that the circulation time is practically normal in the artificial pneumothorax group. They presented no signs of respiratory or circulatory insufficiency. Dyspnea was felt by most of them only on exertion and none of them showed signs of cardiac decompensation.

In the pure anthracosilicotic group the circulation time was normal only in 2 cases. In the tuberculous anthracosilicotic group it was normal in 3 cases. In the rest of the cases in both groups the circulation time was distinctly increased and longer than that found in the artificial pneumothorax group. Dyspnea was not a prominent feature in those in whom the circulation time varied between 11 to 17 seconds. Dyspnea, however, was marked and constant when it was longer than 17 seconds. Cyanosis and edema of the ankles in addition to dyspnea became manifest when the circulation time

was found to be over 30 seconds. Slight dyspnea on exertion felt by those patients with a circulation time no longer than 17 seconds was due to emphysema coexisting with anthracosilicosis whereas marked dyspnea manifesting itself in those having longer circulation time was principally cardiac in origin. In this latter group cardiac enlargement as found by the physical examination, Roentgen ray and necropsy was a frequent finding.

The normal pulmonary circulation time as found in the artificial pneumothorax group and in a few cases of the anthracosilicotic group with or without pulmonary tuberculosis does not necessarily indicate that the pulmonary circulation in these cases is normal. The circulation time in these cases is no index of the volume of blood-flow through the collapsed, fibrotic or emphysematous lungs. We find that the velocity of fluid flowing through a shorter and narrower tube is faster than through a longer and wider tube. The quantity of fluid, however, passing through a larger and longer tube is greater. We know that in anthracosilicotic lungs with or without pulmonary tuberculosis and also in collapsed lungs, the vessels become narrowed and shortened due to sclerosis. In the absence of myocardial weakness, the velocity of bloodflow through such vessels may be practically normal but the volume flow will be less. In view of this, the absence of toxic symptoms in many cases of anthracosilicosis in association with pulmonary tuberculosis, as pointed out by Landis,² and amelioration of symptoms in satisfactory artificial pneumothorax cases may be in part due to decrease in the volume of bloodflow through the diseased lung.

Summary and Conclusion. 1. The pulmonary circulation is studied in pulmonary tuberculosis treated with artificial pneumothorax, pure anthracosilicosis and anthracosilicosis associated with tuberculosis.

2. Pulmonary circulation time is practically normal in artificial pneumothorax but usually prolonged in anthracosilicosis with or without pulmonary tuberculosis due largely to cardiac weakness.

3. It is suggested that regardless of normal circulation time in the artificial pneumothorax group and in a few cases of the anthracosilicotic group with or without pulmonary tuberculosis the volume of bloodflow through the diseased lungs may be decreased.

The writers desire to tender their thanks to Dr. Frank A. Craig and to Dr. Joseph Walsh for their valuable criticisms and permission to use the sanatorium material.

BIBLIOGRAPHY.

- (1.) Charr, R.: Unpublished data. (2.) Landis, H. R. M.: *Diseases of the Chest*, W. B. Saunders Company, Philadelphia, p. 535, 1929. (3.) Winternitz, M., Deutsch, J., and Brull, Z.: *Med. Klin.*, 27, 986, 1931.

ANGIOSPASTIC CLAUDICATION.*

WITH A REPORT OF SIX CASES.

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ONE of the most frequent complaints of patients who suffer from arterial disease is claudication. By claudication is meant any pain or cramp, often in the calves, sometimes in the toes or soles, less often in the thighs, initiated by exercise, and relieved promptly by rest. In addition, the patient may have other signs or symptoms of arterial insufficiency. Color changes of digits, trophic changes in the skin, nails and subcutaneous tissue, diminution of palpable arterial pulsations, decrease in temperature of the part, ischemia on elevation, rubor on dependency, and finally gangrene, all mark the extremity suffering from insufficient blood supply.

Differentiation Between Spasm and Occlusion as Factors in Peripheral Arterial Disease. Having determined that the peripheral arteries are at fault, the next problem is to decide whether the failing circulation is due to organic occlusion of vessels, to pure vasospasm, or to a combination of the two. This is determined by the accurate measurement of surface temperature by means of a thermocouple (Scott⁶), noting the temperature variations during vasomotor paralysis. It is now known that the sympathetic vasoconstrictor fibers do not pass to their areas of distribution with the blood-vessels. They accompany for the most part the peripheral sensory nerves, and supply areas very closely approximating the peripheral cutaneous sensory distribution.⁹ Ablation of vasoconstrictor influence may be obtained by various methods. Among these may be mentioned 1, subarachnoid block; 2, conduction block of peripheral nerves;^{7a,b} 3, sympathetic nerve block;⁸ 4, general anesthesia;^{7a} 5, use of high environmental temperature,¹ and 6, by soaking the upper extremities (for testing the feet) or the lower extremities (for testing the hands) in water at 43 to 45° C. This Clinic has had experience with only the first three methods, mostly, however, with conduction block of peripheral nerves, and thinks that peripheral nerve block is more logical from a theoretical standpoint, more desirable from the practical standpoint, and gives more consistently reliable information from the clinical standpoint, than other tests. Our experiences with this method and a fuller discussion of these points will be reported in an article to follow. When total vasoconstrictor paralysis has been induced in normal individuals the surface temperature of the affected regions rises to a certain level,

* Read in part, before the San Francisco County Medical Society, August 14, 1934.
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irrespective of the original temperature. This is called the "normal vasodilatation level,"^{7a} and is remarkably constant for the type of vasomotor study employed.

The response of the body to gradual arterial occlusion is the ablation of vasoconstrictor influence. This does not seem to occur in cases of arteriospasm. In individuals suffering from pure vasospasm, the surface temperature after novocaine block or general anesthesia rises to the normal vasodilatation level. In those suffering from pure occlusion there is little or no rise of surface temperature. In the combination of spasm and occlusion, there is a variable rise of temperature which is in direct proportion to the amount of spasm present.^{4, 7b} The difference between the maximum temperature obtained and the normal vasodilatation level is called the "occlusion index."^{7a} The treatment varies in accordance with these findings.⁴ In the author's experience, the response of skin temperatures, properly controlled and measured, is a most reliable index of the vasoconstrictor element. There may be diminution or absence of arterial pulsations in the foot and yet one may obtain a normal vasodilatation level. In such cases, if the pulsations become normal after vasoconstrictor paralysis, arteriospasm was undoubtedly the cause of the diminished pulsations. If the pulsations are unchanged in the presence of a normal vasodilatation level, it is probable that the collateral vessels are under vasomotor control to the point of permitting normal vasodilatation.

In differentiating the claudication due to arteriospasm from that due to arterial occlusion it is assumed that the presence of a normal vasodilatation level is sufficient evidence of the ability of the arterial tree to dilate to the same extent as occurs in vasoconstrictor paralysis in normal subjects. Although there is no doubt that the skin temperatures are directly proportional to the amount of blood flowing through the part, this gives no information as to the circulatory responses of the deeper tissues.

The pain of claudication is at times referred over sympathetic pathways.^{2, 5a, b} Blocking directly the sympathetic chain at the proper level gives information not only as to the presence or absence of occlusion, but also as to whether pain is referred over this system.⁸

In the past, the term claudication has been practically synonymous with occlusive disease. In examining a considerable number of cases complaining of claudication, I have found 6 which were on an arteriospastic basis. The clinical picture was similar in all.

Case Abstracts. CASE 1.—C. S., a Russian housewife, aged 53, for the past year complained of claudication in both calves after walking exactly 1 block on the level, worse on the left side. She is a diabetic of 20 years' standing and also has high blood pressure.

Examination. All vessels of the lower extremities have normal pulsations except the right posterior tibial, which cannot be felt. There is a slight elevation ischemia on both sides, but no dependent rubor. Roentgen-rays show very slight calcification of the foot vessels on the right; moderate

on the left. However, in view of these excellent pulsations and the subsequent tests, the Roentgen ray findings are probably not significant. Claudication was induced on the left. During the pain, the toes were white and cadaveric, and the dorsalis pedis artery could not be palpated. After 1 minute rest, the pain disappeared and the normal color returned; soon afterward the dorsalis pedis pulsation could again be felt normally.

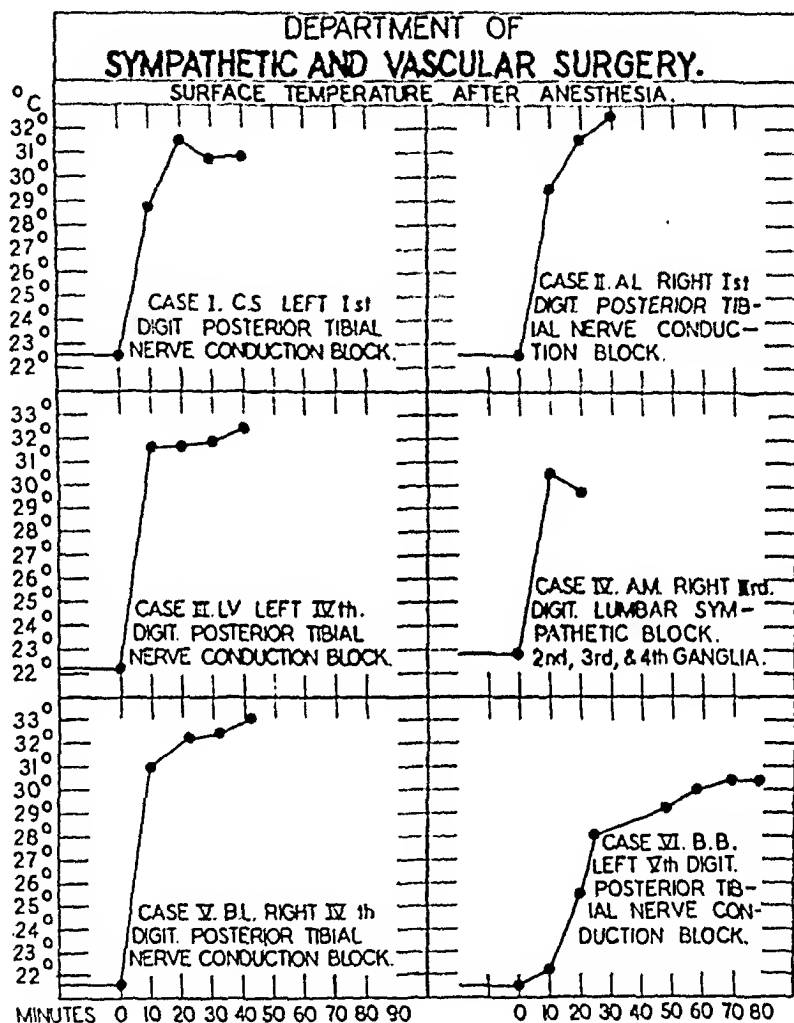


CHART I.—Vasomotor studies on cases reported. The normal vasodilatation level for peripheral nerve conduction block is 30.5° C. That for sympathetic block is 31.5° C. The normal curve is a steep rise to the normal level. Slow rises are suggestive of arterial occlusion. The element of vasoconstrictor spasm is marked in each case.

There were normal vasodilatation responses to controlled posterior tibial nerve block in each foot (Chart I). This indicated that the symptoms were not due to arterial occlusion. One week later, during the vasodilatation following novocaine block of the left 2d, 3d and 4th lumbar sympathetic ganglia, she walked without pain, and it was impossible to produce ischemia of the foot or decrease of foot pulses by exercise. After 1½ hours, the vaso-

dilatation disappeared, and the condition present before injection returned. She failed to report for treatment.

CASE 2.—A. L., a Russian housewife, aged 67, complained of claudication in both calves after walking exactly $2\frac{1}{2}$ level blocks. For the past 20 years, she has had a marked swelling of both legs which is worse after walking and at night. She also suffers from hypertensive heart disease.

Examination. Revealed a brownish discoloration and swelling of the ankles and the lower half of both legs of the lymphatic type. No pulses were palpable in either foot. Both popliteal arteries had diminished pulsations. The femoral arteries pulsated normally. There was moderate elevation ischemia and mild dependent rubor in both feet. The right foot and lower leg were colder than the left, the change occurring abruptly 3 inches above the ankle.

Claudication was induced in both calves by exercise. Immediate inspection showed marked local ischemia of the lower two-thirds of both feet. As the pain disappeared the feet resumed the normal color. There was a normal vasodilatation response to bilateral posterior tibial nerve block (Chart I), showing that the symptoms were not due to occlusive arterial disease. During vasodilatation both dorsalis pedis and both posterior tibial arteries became palpable. Roentgen rays showed no calcification of leg or foot arteries.

The claudication was probably due to a pure arteriospasm. Diathermy to the lumbar sympathetics was advised, but she elected to go to a warmer climate for 2 weeks. She was considerably improved on her return and could walk 6 blocks without pain. Examination showed ischemia of the toes during the pain of claudication, as before. She took diathermy for 3 weeks and could then walk 9 blocks.

CASE 3.—B. B., male, aged 48, for the past 3 months has had attacks of dull cramp-like pain which began just below the knee posteriorly and extended to the front of the leg and finally the foot. The foot then became numb, helpless, and felt swollen. He was forced to rest. The symptoms were initiated only by exercise and relieved in about 30 seconds by rest; they occurred in either foot, but never both feet simultaneously. He can now walk only 1 level block rapidly. His work necessitates the carrying of heavy ice-cream freezers weighing as much as 75 pounds up many flights of steps daily. These attacks have caused him to discontinue employment.

Examination of the Extremities. The right popliteal pulse was diminished. All other pulsations were normal. The strength of the dorsalis pedis pulse was variable. There was no ischemia on elevation or rubor on dependency. Controlled thermocouple readings showed no abnormal temperature differences. Following posterior tibial nerve block, there were normal vasodilatation levels in both feet (Chart I), showing that symptoms were not due to vascular occlusion. During vasodilatation the dorsalis pedis pulsations increased, and he was able to climb rapidly four steep flights of steps without symptoms, whereas previously he could only climb one or two flights. Later, claudication was induced on the right. Prompt examination showed the right foot waxy, blanched, and cadaveric, and no pulsation of its dorsalis pedis; the left foot was slightly blanched and its dorsalis pedis diminished. One minute later the symptoms disappeared, the right foot resumed its normal color, and a few seconds later the dorsalis pedis could again normally be felt. Both feet were immersed in water at 16° C. for 10 minutes. Both remained pink. Claudication was again induced. The picture of ischemia again appeared on the right, whereas the left foot remained pink in marked contrast. The claudication in this patient is shown by the studies detailed above to be due to arteriospasm. Lumbar ganglionectomy was advised, but the patient refused. He has not returned since.

CASE 4.—A. M., male, aged 62, complained that for the past 3 months he has had claudication in both calves after walking 2 level blocks, worse on the right side. He has had flat feet, but was not relieved by arch supports fitted by an orthopedist. Several months ago, ulcers appeared on his legs and feet. These healed only a short time ago. He has had varicose veins of both legs for years.

Examination. On the *right side* the pulsation of the dorsalis pedis artery was slightly diminished, the posterior tibial absent, and the popliteal and femoral normal. There was slight elevation ischemia and mild dependent rubor of the anterior two-thirds of the foot. On the *left side* the pulsation of the dorsalis pedis, popliteal, and femoral arteries was normal; the posterior tibial was not felt. There was normal color on elevation; slight rubor on dependency, less than on the right. Neither leg had ulcers or gangrenous areas, but scars of the old ulcers were present on both legs and both feet. Both legs were the site of marked varicose veins, in some of which were areas of calcification.

Claudication was induced on the right by exercise. Coincident with its onset the right foot became blanched and the pulsation of its dorsalis pedis artery imperceptible. As the cramp subsided the color and the pulsation returned. There was no change in the color or the pulsations of the left foot; during exercise it retained the mild erythemia found on dependency.

A few days later, the second, third, and fourth right lumbar sympathetic ganglia were blocked with novocaine. During vasodilatation (Chart I), he jumped until exhausted, but neither claudication nor color changes appeared. After a slight rest he was also able to walk up three flights of building steps until exhausted, but had no cramps in his legs. These studies indicate that symptoms were probably due to arteriospasm. He refused diathermy and vasodilating drugs and has not been heard from since.

CASE 5.—B. L., a married woman, aged 70, for the past year complained of claudication in both legs, especially the left after walking one level block. Her feet have felt cold recently. There has been no ulceration or gangrene.

Examination. Showed the pulsation of both dorsalis pedis arteries present but slightly diminished, the left more so than the right. The posterior tibial arteries were not felt. The popliteal artery was not felt on the left; it was barely palpable on the right. Both femoral pulsations were normal. There was mild ischemia of the feet on elevation, but no rubor on dependency. During claudication, the feet were found to be cadaveric, the foot pulses absent. Normal color returned after 2 minutes' rest, but the pain was not relieved until about 3 minutes later when the foot pulses were again palpable.

There was a normal vasodilatation response (Chart I) on both sides to posterior tibial nerve block. Roentgenograms showed no calcification of foot vessels. A few days later, the second, third, and fourth lumbar sympathetic ganglia of both sides were blocked with novocaine. During the vasodilatation, she walked five blocks without pain. As soon as the vasodilatation disappeared she could walk only a half block without pain.

The above studies show that the claudication occurred in extremities capable of full vasodilatation and therefore it was primarily of a spastic nature. She obtained no relief from 3 weeks of diathermy to the lumbar sympathetics and did not report for 9 months when she complained of increased severity of claudication during the past 6 months. She could hardly walk at all. Both feet became numb and tingled, these symptoms progressively spreading up the calf. She had severe cramps at night. Examination showed no vessels palpable below the femorals in both lower extremities. The femoral pulses were slightly diminished. There was slight rubor of the right toes on dependency, otherwise no other abnormal vascular signs. The feet were warm. Vasomotor studies were repeated using pos-

terior tibial nerve block as before. Comparison with results of the 1934 test showed that the digits of the left foot reached a level only from 0.1 to 0.7° C. below that of 1934, whereas those of the right foot were from 2.9 to 3.6° C. below the 1934 level. Occlusive indices on the right ranged from 0.5 to 3.3. Roentgen rays of the feet, which were negative in 1934, showed barely perceptible calcification of the dorsalis pedis arteries. There was no question but that there was a change for the worse on the right side, and that the element of spasm was receding. On August 14, 1936, the right second, third, and fourth lumbar sympathetic ganglia were blocked with absolute alcohol. She was confined to bed since the injection because of severe pain due to the alcohol and entered the hospital September 1, 1936. The surface temperature rise following the injection was still present, and she had an anhidrosis of the entire right lower extremity and hyphidrosis of the left thigh. Since the alcohol injection she had been confined constantly to bed because of severe pain and is now (October 30, 1936) failing rapidly. It was therefore impossible to determine the effect of the alcoholic injection in this patient on her claudication.

CASE 6.—A man, aged 80, complained that for the past 8 years he has had claudication in the left calf after walking 1 level block. For several months he has had attacks of numbness of the left leg. The femoral artery was faintly palpable on the left. All other arteries of this extremity were not felt to pulsate. On the right the femoral artery pulsation was normal, the popliteal was much diminished, and the foot artery pulsations were absent. There was no change on elevation, but on dependency rubor was slight to the ankle on the right, moderate to the ankle on the left. There were marked varicose veins on the right, slight on the left. On exposure of the feet to a constant room temperature of 70° for $\frac{1}{2}$ hour there was a blotchy cyanosis of both feet from the ankle to the toes. The toes were markedly blanched. Posterior tibial nerve block on the left showed a normal vasodilatation level in the fifth toe, and very small occlusion indices on the other toes, ranging from 0.5 to 2.1 (Chart I). The arteries of the foot did not pulsate during the vasomotor block. Roentgen rays of both feet showed no arterial calcification. These studies indicated that arteriospasm was the factor of importance in the production of symptoms. Because of myocarditis and arterial hypertension, it was considered unwise to subject him to the exercise test. After 10 diathermy treatments to the lumbar spine the claudication disappeared. The patient died about 2 weeks later of pneumonia complicating a severe carbuncle of the neck.

This case is one in which a high vasodilatation level was present in all toes. Although Roentgen rays failed to show arterial calcification, there is a slight degree of arterial insufficiency as shown both in the absence of foot pulsations, and the response to nerve block. Arteriosclerotic degeneration may produce occlusion without calcification. In any event the ability of the arteries, either major or collateral, to dilate is amply shown by the response to vasomotor paralysis; the symptom of claudication must therefore be due primarily to arteriospasm.

Discussion. These cases had in common the symptom of claudication. The onset of claudication was associated with diminution of arterial pulsations and acute ischemia of the part. Relief was associated with return of the previous color and of palpability of pulses. All had normal or nearly normal vasodilatation levels. Roentgen rays usually showed no arterial calcification.

In 1932, Morton and Scott⁴ reported 8 cases of claudication associated with normal or nearly normal vasodilatation levels;

5 were in cases of thrombo-angiitis obliterans; 1 had no evidence of organic arterial disease; 1 had definite evidence of arterial disease without evidence of calcification by Roentgen ray; and the last had definitely calcified foot and leg arteries with undoubted signs of occlusive arterial disease. No mention was made of the behavior of the foot pulses or the occurrence of color changes of the feet coincident with claudication or immediately after the cessation of claudication.

In none of the cases reported herein, was there evidence of thrombo-angiitis obliterans. Some cases showed evidence of organic arterial disease. Angiospastic claudication may occur in patients who have no organic arterial disease, and it may also occur as a symptom of early organic arterial disease. My Case 5 is a case in point.

The following data were obtained from the analysis of the 6 cases reported herein (Table 1). Their average age was 63.3 years. There were 3 males, 3 females. Tobacco was not used by 4 patients, moderately used by 2. The average duration of symptoms was 27 months; only 2 had symptoms for over a year. Moderate elevation ischemia was noted in both extremities in 3 cases, in one extremity in 2 cases; it was absent in only 1 case. Mild rubor was present in 4 cases; in all but 1 it was bilateral. There was a history of ulceration in 1 (A. L.); in this case, varicose veins may have been the prime factor. No case had gangrene, past or present. The dorsalis pedis arteries were palpable in 5 cases, in 1 (A. L.) only after nerve block. The posterior tibial arteries were palpable in 3 cases; 1 unilaterally, 1 bilaterally, and 1 (A. L.) only during vasoconstrictor paralysis. There was no constant relationship between the side of more pronounced symptoms and the palpability of vessels. Varicose veins were present in 3 cases. Roentgen rays of the feet were taken in 4 cases; in 3 there was no visible calcification; in 1 (C. S.) there was mild calcification probably of little significance. Lumbar sympathetic novocaine block was done on 3 cases; in each of these the symptoms were relieved during the block. One case (B. B.) was relieved during posterior tibial nerve block.

In analyzing the significance of arterial pulsations, one should remember that there is a variation which is within normal limits. In my experience the presence and strength of the pulsation of the dorsalis pedis artery is the most reliable. The posterior tibial artery is the most variable, and its diminution or absence is not so significant as that of the dorsalis pedis artery. The popliteal artery is often difficult to feel, but its presence is more constant in normal extremities than the posterior tibial.

Treatment. Treatment should at first be conservative. Two of my cases obtained relief from diathermy to the lumbar region. Vasodilating drugs should be tried. Tobacco should be eliminated.

TABLE 1.—CASE DATA.*

Case.	Asc.	Sex.	Tobacco.	Duration of claudication.	Walking distance → claudication.	Side.	Intensity of symptoms.	Elevation ischemia.	Dependent rubor.	Sudden temp. change.	Trophic dist.	Color changes.	Ulceration.	Gangrene.	Arterial pulsations.				Occlusive index.	Varicose veins.	Edema.	Calcification of arteries in Roentgen ray.	Effect of elaudication on		Effect of vasomotor paralysis on symptoms.
															Dorsalis pedis.	Post. tibial.	Popliteal.	Femoral.					Appearance of foot.	Dorsalis pedis pulse became	
1	S.	53 F	0	1 yr.	One level block	R	+++	+	0	0	Nails	0	0	0	+++	0	+++	+++	0	0	0	+	Not tested	0	Effect of vasomotor paralysis on symptoms.
2	A. L.	67 F	0	2½ mo.	2½ level blocks	R	+++	+	+	0	0	Brown discoloration of ankles	0	0	0	0	+++	+++	0	++	0	++	Cadaveric ischemia of toes coincident with claudication. Return of normal color with relief	0	Impossible to produce claudication, pulse changes, or ischemia during lumbar sympathetic novocaine block.
3	B. B.	48 M	½ cigarets daily	10 mo.	1-2 flights steps with load	R	+++	+	+	0	0	0	0	0	0	0	+++	+++	0	++	Lym. +++ type	0	Ischemia both feet. Return normal color with relief of claudication	0	Dorsalis pedis and post tibial pulses became palpable +++ during vasomotor paralysis.
4	A. M.	62 M	40 cigarettes daily	3 mo.	2 level blocks	R	+++	+	+	0	0	0	0	0	++	0	+++	+++	0	++	0	0	Cadav. isch. of foot coinc. with claud. Return normal color with relief.	0	Dorsalis pedis pulse +++ during vasomotor paralysis. Unable to produce claudication, pulse changes or ischemia during vasomotor paralysis.
5	B. L.	70 F	0	1 yr.	One level block	R	+++	+	+	0	0	0	0	0	++	0	+++	+++	0	++	0	0	Cadaveric ischemia of foot coincident with claudication. Return of normal color with relief	0	Unable to produce claudication, pulse changes or ischemia during lumbar sympathetic. novo. block.
6	J. C.	80 M	8 yrs.	8 yrs.	One level block	R	0	+	+	0	0	0	0	0	0	0	+++	+++	Not determined	+++	0	0	Test not done because of bad heart	0	Test not done.
						L	+++	0	++	0	0	0	0	0	0	0	0	+	0 to 2.1	+	0	0	Test not done because of bad heart	0	Test not done.

* 0 = symptom absent, sign absent, pulsation absent.
 + = symptom slight, sign mild, pulsation barely felt.
 +++ = symptom moderate, sign moderate, pulsation easily felt, but below normal force.
 ++++ = symptom severe, sign marked, pulsation normal.

The extremities should be kept warm constantly. If conservative measures fail and the symptoms are incapacitating, the lumbar sympathetic ganglia should be blocked with novocaine for diagnostic purposes. If this brings relief, lumbar ganglionectomy is advised. Vasomotor studies should be done every 3 months. Roentgen rays of foot vessels should be taken every 6 months. If the vasodilatation level recedes, lumbar ganglionectomy should be done to promote collateral circulation and to prevent as far as possible the occurrence of organic arterial insufficiency. Alcoholic injection of the lumbar sympathetics may be used in place of ganglionectomy in patients who are poor risks for surgery, but often the disability resulting from alcohol injection is much greater than that resulting from surgery.

Summary. 1. Six cases are reported in which the symptom of claudication was shown to be due to arteriospasm.

2. The onset of claudication is associated with acute ischemia of the foot and diminution or absence of foot pulsations; relief is associated with return of normal color and palpability of foot arteries.

3. All cases have normal or nearly normal vasodilatation responses to properly controlled vasomotor paralysis. In 1 case previously imperceptible foot pulses became palpable during vasomotor paralysis. Evidence indicates that the collateral circulation may be under vasomotor influence to the point of allowing normal vasodilatation.

4. Roentgen rays of the feet were taken in 4 cases. In 3 they showed no calcification of vessels; in 1 there was slight calcification of little significance.

5. Treatment should be conservative. If this fails, the response to diagnostic novocaine block will determine the advisability of lumbar ganglionectomy. The latter procedure should be advised in good risks which are incapacitated by the symptoms and which are relieved by diagnostic block. If vasomotor studies show receding of the vasodilatation level, lumbar ganglionectomy should be done. Poor surgical risks may be treated by alcohol injection of the lumbar sympathetic chain.

6. The term "Angiospastic Claudication" is descriptive of the syndrome and distinguishes it from the claudication of occlusive arterial disease.

REFERENCES.

- (1.) Collier, F. A., and Maddock, W. G.: *Ann. Surg.*, 96, 719, 1932. (2.) Flothow, P. G.: *Northwest Med.*, 9, 408, 1931. (3.) Gibbon, J. H., Jr., and Landis, E. M.: *J. Clin. Invest.*, 11, 1019, 1932. (4.) Morton, J. J., and Scott, W. J. M.: *Ann. Surg.*, 96, 754, 1932. (5.) Reichert, F. L.: (a) *Northwest Med.*, 31, 554, 1932; (b) *Ann. Surg.*, 97, 503, 1933. (6.) Scott, W. J. M.: *J. Am. Med. Assn.*, 94, 1987, 1930. (7.) Scott, W. J. M., and Morton, J. J.: (a) *Arch. Int. Med.*, 48, 1065, 1923; (b) *J. Am. Med. Assn.*, 97, 1212, 1931. (8.) White, J. C.: *Ibid.*, 94, 1382, 1930. (9.) Woolard, H. H., and Phillips, R.: *J. Anat.*, 67, 18, 1932.

CHANGES IN THE ELECTROCARDIOGRAM AS CRITERIA OF INDIVIDUAL CONSTITUTION DERIVED FROM ITS PHYSIOLOGICAL PANEL.

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OUR earlier published studies of the human organism as a whole dealt chiefly with morphology; and it has been our experience that within limits persons afflicted with the same illness exhibit in common a characteristic morphology. In other words, the nature of the anatomic panel may often indicate a relationship between total personality and disease. We have long considered whether correlations may likewise exist between disease proclivity and characters within the physiologic panel. It seemed possible that certain physiologic techniques which have rendered dependable evidence of pathologic function might also illuminate normal individual differences in the special qualities of separate organs. For surely we must assume that it is the mutual coöperation of these organs which proclaim at once the unity and personal identity of each individual.

Observations bearing on this concept are not new in medicine. Thus, for example, Laignel-Levastine and Maingot⁵ described various forms of diaphragmatic motion, as seen by fluoroscope, which showed high correlation with the nature of the whole man and his special disease potential. Speaking of diaphragmatic movements they state: "There exists an internal physiognomy which from the standpoint of individuality surpasses the external. External gestures are consciously appreciated and controlled; the spontaneous movement of the diaphragm is subconscious." According to Nielsen and Roth,⁶ spiograms can be used to identify at least nine different types of persons. Many of these spiogram patterns are hereditary and indicate certain predispositions in the person.

Cardiologists have known that the form of the electrocardiographic curve, and the time relationship of its component parts, correlates with age. Furthermore, Cohn and Swift² state that the general form of the electrocardiogram is relatively constant in normal persons over long periods of time. In his Nobel prize oration, also, Einthoven,⁴ showed that if there had been no change in the heart's condition during long periods of months, or even years, the electrocardiographic records were practically identical. He illustrated this by two records taken 31 years apart from a patient who had an unchanging lesion for that whole period of time (Fig. 1). Cohn² has kindly supplied us with the records shown in Figures 2 and 3.

In the records of 1933, 1936 and 1937 the 3 leads were synchronously recorded by the use of 3 galvanometers. Apparently the recorded voltage is in every case slightly lower by this technique than when each lead is taken separately as in the earlier electrocardiograms. In each case the adherence in the later record to the individual's initial pattern is clear. Only in the *T'* wave, which is perhaps the most labile component in the whole complex do striking variations appear. In Figure 2 (Case 3) a difference in the relative positions of the *Q* and *S* waves also appears. Whether it can be said that an electrocardiogram is unique for each person, or perhaps for a type of human being, is a question. At least there is at present little information available on the point.



FIG. 1.—Einthoven's comparison of capillary electrometric curve taken 1894 (Lead I), and Ekg (Lead I) of same case taken 31 years later, in 1925.

Method. In order to test the possibility that the electrocardiographic record might provide a criterion of constitution from the physiologic panel, two groups of invalids, peptic ulcer and gall bladder, all having normal electrocardiograms were studied.

For control observations on age variation of the *P-R* and *Q-T* intervals, as well as pulse rate, the electrocardiograms of 578 individuals with normal records, selected from the general hospital population both male and female, were used. These were divided into 6 age decades, from 10 to 69 (Table 1). All calculations in the tables are for convenience expressed in terms of the actual value times 100. For the comparative study of ulcer and gall-bladder patients only males are being reported upon at present.

In the ulcer series there are 107 persons divided into 4 age decades, from 20 to 59 years. The decade groups though small are nevertheless sufficiently large for statistical validity. In the gall-bladder series there are only 35 males in all.

The *P-R* Interval. It is apparent from Figure 4 that among hospital males with normal electrocardiograms there is a gradual lengthening of the *P-R* interval up to and including the sixth decade. In the seventh decade there is a shortening again, but barely of statistical significance. The female curve follows almost the same line until the sixth decade. At this time, unlike the males, the *P-R* interval becomes shorter so that as between males and females in the sixth decade there is a significant difference*

* A difference between two compared means is significant when that difference is three or more times its probable error.

in the mean length of the $P-R$ interval (Table 2). In the seventh decade the female curve rises again well above that of the males though not significantly.

The behavior of the $P-R$ interval in the ulcer people is striking. Thus in the third decade the difference between the ulcer group

TABLE 1.—COMPARISON OF $P-R$ INTERVALS OF HOSPITAL MALE AND FEMALE AGE GROUPS AND ULCER AND GALL-BLADDER AGE GROUPS.

Group. Male.	Age in years.	No. of cases.	Range.	Mean and P.E.* (hundredths of seconds)	S D* and P.E.	V* and P.E.
Hosp.	10-19	40	12-19	14.78 \pm 0.17	1.56 \pm 0.12	10.55 \pm 0.80
Hosp.	20-29	35	12-19	15.29 \pm 0.22	1.89 \pm 0.15	12.36 \pm 1.00
Hosp.	30-39	43	13-20	15.58 \pm 0.14	1.40 \pm 0.10	8.98 \pm 0.65
Hosp.	40-49	40	12-20	15.95 \pm 0.18	1.67 \pm 0.13	10.47 \pm 0.79
Hosp.	50-59	51	12-19	16.33 \pm 0.14	1.48 \pm 0.10	9.06 \pm 0.60
Hosp.	60-69	54	12-19	15.70 \pm 0.16	1.69 \pm 0.11	10.76 \pm 0.70
Total male	..	263	12-20	15.65 \pm 0.07	1.69 \pm 0.05	10.80 \pm 0.32
Ulcer	20-29	20	13-20	17.00 \pm 0.30	2.02 \pm 0.22	11.88 \pm 1.27
Ulcer	30-39	44	13-22	17.14 \pm 0.21	2.10 \pm 0.15	12.25 \pm 0.88
Ulcer	40-49	23	13-18	16.04 \pm 0.17	1.20 \pm 0.12	7.48 \pm 0.74
Ulcer	50-59	20	13-19	16.45 \pm 0.25	1.66 \pm 0.18	10.09 \pm 1.08
Total ulcer	..	107	13-22	16.75 \pm 0.12	1.90 \pm 0.09	11.34 \pm 0.52
Total gall bladder	30-59	35	13-20	15.66 \pm 0.19	1.70 \pm 0.14	10.86 \pm 0.88
Female.						
Hosp.	10-19	59	12-19	14.70 \pm 0.13	1.49 \pm 0.09	10.14 \pm 0.63
Hosp.	20-29	60	12-19	15.02 \pm 0.14	1.64 \pm 0.10	10.92 \pm 0.67
Hosp.	30-39	54	12-20	15.94 \pm 0.18	1.93 \pm 0.12	12.11 \pm 0.79
Hosp.	40-49	56	12-19	15.68 \pm 0.17	1.85 \pm 0.12	11.80 \pm 0.75
Hosp.	50-59	49	12-20	15.57 \pm 0.18	1.87 \pm 0.13	12.01 \pm 0.82
Hosp.	60-69	37	12-19	16.24 \pm 0.19	1.73 \pm 0.14	10.65 \pm 0.84
Total female	..	315	12-20	15.46 \pm 0.07	1.83 \pm 0.05	11.84 \pm 0.32

* P.E. = Probable error; S.D. = Standard deviation; V = Variation.

TABLE 2.—DIFFERENCES OF MEANS OF MALE AND FEMALE SUBGROUPS WITH VALUE IN TERMS OF THE PROBABLE ERROR.

		Female*	
		Male	
Subgroup.		Difference.	X P.E.
<i>P-R Interval.</i>			
Age 10-19	-0.08	-0.38
Age 20-29	-0.27	-1.04
Age 30-39	+0.36	+1.56
Age 40-49	-0.27	-1.07
Age 50-59	-0.76	-3.30
Age 60-69	+0.54	+2.16
Total	-0.19	-1.90
<i>Q-T Interval.</i>			
Age 10-19	-0.33	-1.06
Age 20-29	-0.36	-0.90
Age 30-39	-0.49	-1.40
Age 40-49	-0.26	-0.72
Age 50-59	-0.92	-2.70
Age 60-69	-0.58	-1.45
Total	-0.66	-4.12
<i>Pulse Rate.</i>			
Age 10-19	+5.90	+4.01
Age 20-29	+5.95	+3.63
Age 30-39	+4.80	+2.80
Age 40-49	+3.10	+2.15
Age 50-59	+5.90	+3.62
Age 60-69	+0.60	+0.34
Total	+4.45	+6.64

* In this and other similarly expressed fractions the group above the line is compared with that below.

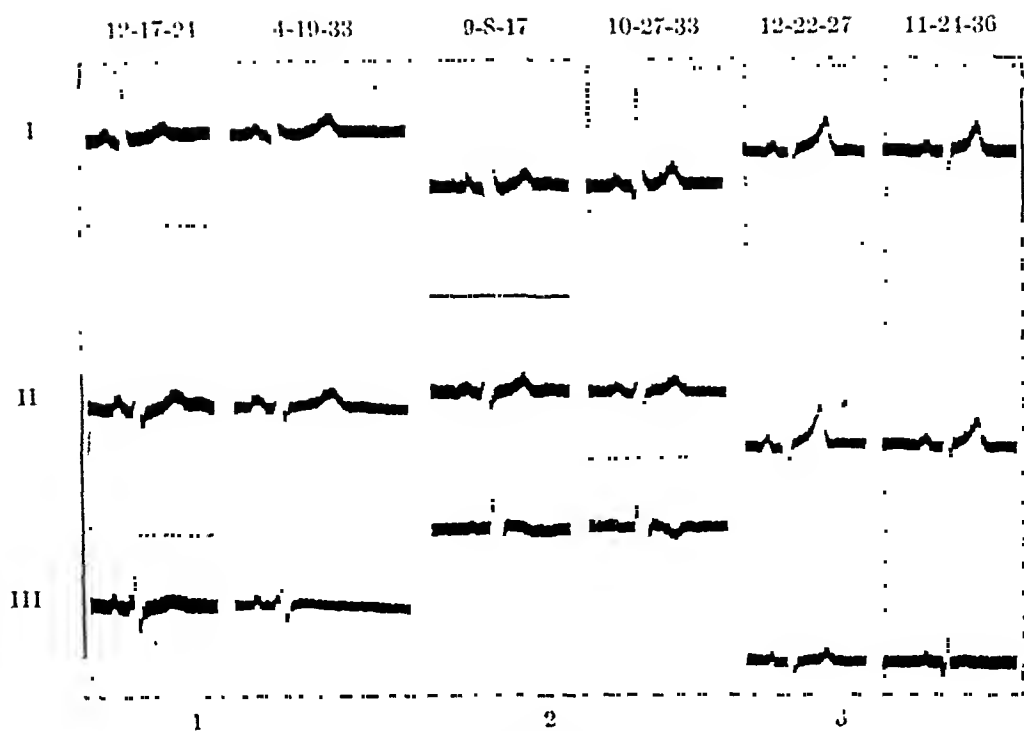


FIG. 2.—Electrocardiograms of 3 subjects, showing constant pattern similarity over 9 to 16 years.

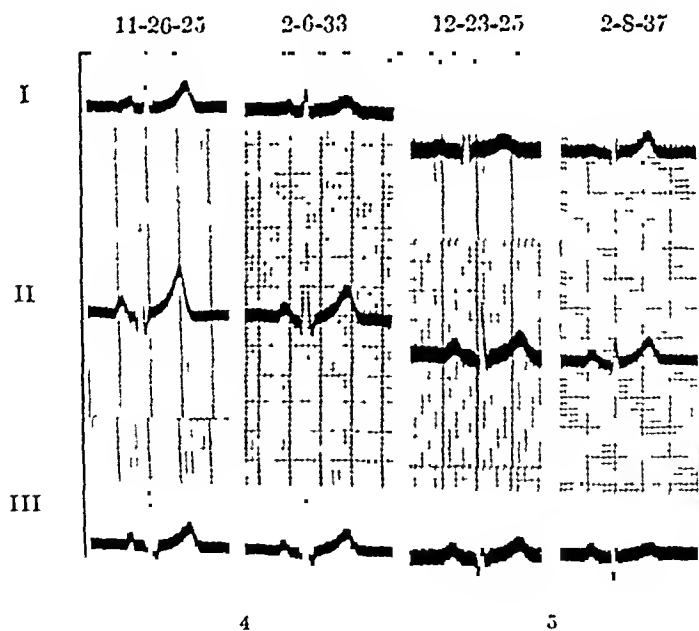


FIG. 3.—Electrocardiograms of 2 patients showing constant pattern similarity over 8 and 12 years.

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mean and control group mean is significant to the extent of being 4.62 times its probable error. In the fourth decade this figure rises to 6.24 times the probable error (Fig. 4 and Table 3). But here a

TABLE 3.--DIFFERENCES OF MEANS OF ULCER AND HOSPITAL MALES IN THE VARIOUS AGE GROUPS WITH VALUE IN TERMS OF THE PROBABLE ERROR.

	Ulcer Hospital		
Age group.	Difference.	N P E.	
<i>P-R Interval.</i>			
Age 20-29	+1.71	+4.62	(Significant)
Age 30-39	+1.56	+6.21	(Significant)
Age 40-49	+0.09	+0.36	
Age 50-59	+0.12	+0.41	
Total	+0.91	+6.50	(Significant)
<i>Q-T Interval.</i>			
Age 20-29	+2.36	+4.14	(Significant)
Age 30-39	+0.81	+2.31	
Age 40-49	+0.46	+1.01	
Age 50-59	+1.69	+3.60	(Significant)
Total	+1.03	+4.48	(Significant)
<i>Pulse Rate</i>			
Age 20-29	-8.30	-4.05	(Significant)
Age 30-39	-6.15	-3.53	(Significant)
Age 40-49	+0.50	+0.25	
Age 50-59	-11.80	-6.56	(Significant)
Total	-5.85	-5.98	(Significant)

sharp change occurs, and in the fifth and sixth decades we find that the *P-R* interval of the ulcer people returns to the average determined in hospital series.

Because the number of males with gall-bladder disease is too small to divide into decade groups, they have been massed. The mean *P-R* interval for this series which comprises three decades is 15.66. This figure agrees statistically with that for the hospital controls. It appears therefore that ulcer people, especially during the two decades when the onset of the disease is most frequent tend to have significantly long *P-R* intervals, whereas the gall-bladder people do not.

So far as rate is concerned the well-established fact that females in general have faster pulse rates than males is clearly shown in the curves for the hospital controls (Fig. 4). It is interesting that both ulcer and gall-bladder people have pulse rates slower than those of the hospital series. Almost the slowest rates in both groups are found in the youngest age decades. In this connection it is worthy of note that sinus arrhythmia is definitely more common in the third and fourth decade ulcer people than in the same age groups of the hospital control series. One other point of interest concerning pulse rate is the extremely low count in the 50-59 year old ulcer males (Fig. 4 and Table 4).

The Q-T Interval. The *Q-T* interval (Fig. 4 and Table 5) shows a more or less regular lengthening of the period in both sexes through the six decades from 10 to 69 years. Among the controls the difference between the *Q-T* mean value in the second decade and the

TABLE 4.—COMPARISON OF PULSE RATE OF HOSPITAL MALE AND FEMALE AGE GROUPS, ALSO OF ULCER AND GALL-BLADDER AGE GROUPS.

Groups.	Age in years.	No. of cases.	Range.	Mean and P E.	S D and P E.	V and P E.
<i>Male.</i>						
Hosp.	10-19	40	50-100	80.10 \pm 1.02	9.60 \pm 0.72	11.98 \pm 0.90
Hosp.	20-29	35	55- 95	75.30 \pm 1.28	11.20 \pm 0.90	14.87 \pm 1.20
Hosp.	30-39	43	50-100	78.05 \pm 1.37	13.30 \pm 0.97	17.04 \pm 1.24
Hosp.	40-49	40	55-100	75.40 \pm 1.07	10.00 \pm 0.75	13.26 \pm 1.00
Hosp.	50-59	51	50-100	77.30 \pm 1.27	13.45 \pm 0.90	17.40 \pm 1.16
Hosp.	60-69	54	50-105	78.00 \pm 1.30	14.20 \pm 0.92	18.20 \pm 1.18
Total male	..	263	50-105	77.45 \pm 0.52	12.40 \pm 0.36	16.01 \pm 0.47
Ulcer	20-29	20	45- 86	67.00 \pm 1.60	10.60 \pm 1.13	15.82 \pm 1.69
Ulcer	30-39	44	55-100	71.90 \pm 1.07	10.50 \pm 0.75	14.60 \pm 1.05
Ulcer	40-49	23	59-100	75.90 \pm 1.68	11.95 \pm 1.18	15.74 \pm 1.56
Ulcer	50-59	20	42- 84	65.50 \pm 1.28	8.50 \pm 0.91	12.98 \pm 1.38
Total ulcer	..	107	42-100	70.75 \pm 0.72	11.10 \pm 0.51	15.69 \pm 0.72
Total gall bladder	..	35	50- 90	71.55 \pm 1.25	11.00 \pm 0.89	15.37 \pm 1.24
<i>Female.</i>						
Hosp.	10-19	59	50-110	86.00 \pm 1.06	12.05 \pm 0.75	14.01 \pm 0.87
Hosp.	20-29	60	54-100	81.25 \pm 1.02	11.75 \pm 0.72	14.46 \pm 0.89
Hosp.	30-39	54	55-100	82.85 \pm 1.02	11.15 \pm 0.72	13.46 \pm 0.87
Hosp.	40-49	56	50-100	78.50 \pm 0.96	10.70 \pm 0.68	13.63 \pm 0.87
Hosp.	50-59	49	60-100	83.20 \pm 1.03	10.70 \pm 0.73	12.86 \pm 0.88
Hosp.	60-69	37	55-105	78.60 \pm 1.16	10.50 \pm 0.82	13.36 \pm 1.05
Total female	..	315	50-110	81.90 \pm 0.44	11.55 \pm 0.31	14.12 \pm 0.38

TABLE 5.—COMPARISON OF MEANS OF *Q-T* INTERVAL OF HOSPITAL MALE AND FEMALE AGE GROUPS, ALSO OF ULCER AND GALL-BLADDER AGE GROUPS.

Group.	Age in years.	No. of cases.	Range.	Mean and P E.	S D and P E.	V and P E.
<i>Male.</i>						
Hosp.	10-19	40	28-39	33.75 \pm 0.22	2.06 \pm 0.16	6.10 \pm 0.46
Hosp.	20-29	35	30-40	34.54 \pm 0.31	2.69 \pm 0.22	7.79 \pm 0.63
Hosp.	30-39	43	30-42	34.21 \pm 0.25	2.41 \pm 0.18	7.04 \pm 0.51
Hosp.	40-49	40	30-45	35.15 \pm 0.28	2.63 \pm 0.20	7.48 \pm 0.56
Hosp.	50-59	51	29-42	35.41 \pm 0.27	2.86 \pm 0.19	8.08 \pm 0.54
Hosp.	60-69	54	31-47	36.15 \pm 0.30	3.30 \pm 0.21	9.13 \pm 0.59
Total male	..	263	28-47	34.96 \pm 0.12	2.85 \pm 0.08	8.15 \pm 0.24
Ulcer	20-29	20	32-44	36.90 \pm 0.48	3.19 \pm 0.34	8.64 \pm 0.92
Ulcer	30-39	44	29-40	35.02 \pm 0.23	2.24 \pm 0.16	6.40 \pm 0.46
Ulcer	40-49	23	31-40	35.61 \pm 0.34	2.46 \pm 0.24	6.91 \pm 0.69
Ulcer	50-59	20	32-41	37.10 \pm 0.38	2.49 \pm 0.26	6.71 \pm 0.72
Total ulcer	..	107	29-44	35.89 \pm 0.18	2.69 \pm 0.12	7.50 \pm 0.34
Total gall bladder	..	35	32-44	38.17 \pm 0.32	2.79 \pm 0.22	7.31 \pm 0.59
<i>Female.</i>						
Hosp.	10-19	59	28-44	33.42 \pm 0.22	2.50 \pm 0.16	7.48 \pm 0.46
Hosp.	20-29	60	29-41	34.18 \pm 0.25	2.88 \pm 0.18	8.42 \pm 0.52
Hosp.	30-39	54	29-40	33.72 \pm 0.24	2.67 \pm 0.17	7.92 \pm 0.51
Hosp.	40-49	56	28-42	34.89 \pm 0.22	2.40 \pm 0.15	6.88 \pm 0.44
Hosp.	50-59	49	31-39	34.49 \pm 0.21	2.14 \pm 0.14	6.20 \pm 0.42
Hosp.	60-69	37	28-39	35.57 \pm 0.26	2.39 \pm 0.19	6.72 \pm 0.53
Total female	..	315	28-44	34.30 \pm 0.10	2.62 \pm 0.07	7.64 \pm 0.20

average for the whole age span is significant. This is also true of the seventh decade (Table 6). Among the ulcer people those in the third decade show a significant lengthening of the *Q-T* interval. But this is not so in the 30-39 age group. In this connection it will be observed that at this age period there is no parallel change in the *P-R* value which remains high (Fig. 4 and Table 3).

Among gall-bladder people, however, an extremely long *Q-T*

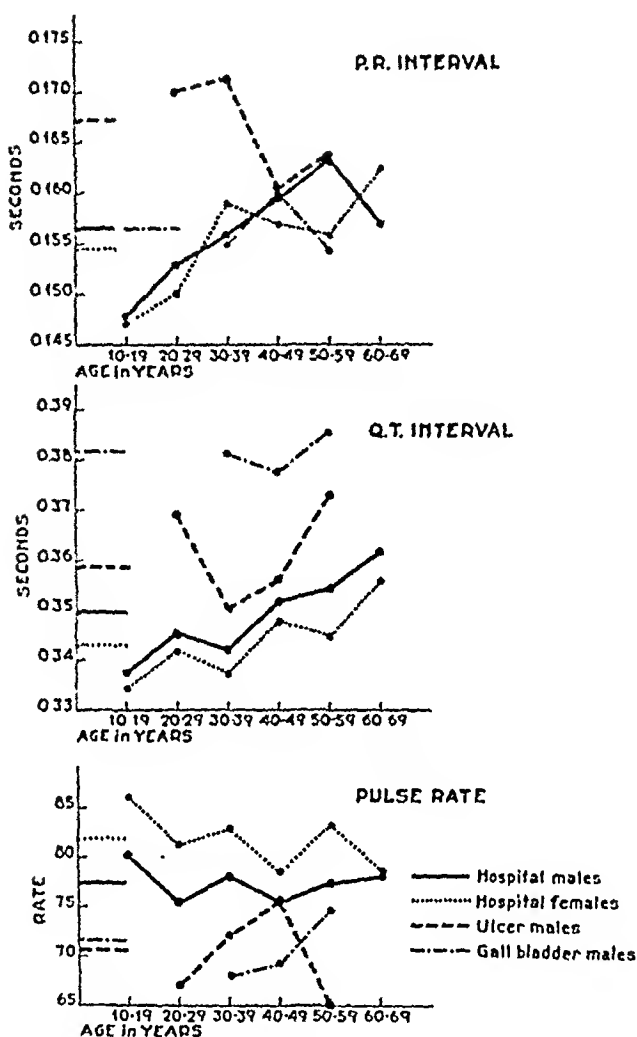


FIG. 4.—The *P-R* and *Q-T* interval and the pulse rate means of normal (male and female) and of ulcer and gall-bladder males electrocardiograms showing changes through six decades. Note: The short horizontal sample key lines at the left of the graphs indicate the means of each total series.

TABLE 6.—DIFFERENCES OF *Q-T* INTERVALS OF HOSPITAL CONTROL SUBGROUPS WITH VALUE IN TERMS OF THE PROBABLE ERROR.

Subgroup.	Subgroup Total Series	Difference.	X P E.
<i>Male.</i>			
Age 10-19		-1.21	-4.03 (Significant)
Age 20-29		-0.42	-1.31
Age 30-39		-0.75	-2.59
Age 40-49		+0.19	+0.63
Age 50-59		+0.45	+1.67
Age 60-69		+1.10	+4.58 (Significant)
<i>Female.</i>			
Age 10-19		-0.88	-3.82 (Significant)
Age 20-29		-0.12	-0.52
Age 30-39		-0.58	-2.42
Age 40-49		+0.59	+2.46
Age 50-59		+0.19	+0.76
Age 60-69		+1.27	+4.38 (Significant)

interval is the striking characteristic. The mean of this measurement for the whole group of 35 individuals spanning third, fourth and fifth decades is 0.382 sec. The difference between this figure and the mean for the same age groups of the hospital control series is 9 times its probable error (Fig. 4, Table 7). This is a high degree of significance and can in no way be attributed to chance.

TABLE 7.—DIFFERENCES OF MEANS OF GALL-BLADDER MALES AND HOSPITAL MALES WITH VALUE IN TERMS OF THE PROBABLE ERROR.

	Gall-bladder Males, Age 30-59	Hospital Males, Age 30-59	
			Difference.
P-R interval	-0.32	-1.52
Q-T interval	+3.22	+9.20 (Significant)
Pulse rate	-5.39	-3.74 (Significant)

ULCER

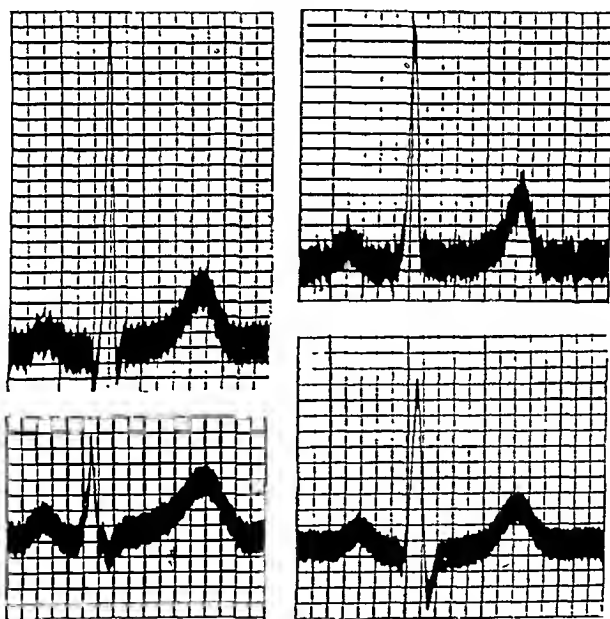


FIG. 5.—Comparison of complex forms (Lead II) from ulcer and gall-bladder people.

Aside from the measurable parts of the electrocardiograms, it is possible we believe to recognize differences of contour between those from ulcer and those from gall-bladder subjects. In general, the form of the curve from ulcer people is steeper, more abrupt; whereas the waves in those from gall-bladder people give the impression of being smoother and more rolling in character (Fig. 5). The descending limb of the T waves perhaps best emphasizes this point. In the ulcer group the descent is very steep; in the gall-bladder subjects

its downward slant is more gradual. In this respect the *T*-wave form of the latter group suggests that seen in records from persons afflicted with hyperthyroidism.*

TABLE 8.—DIFFERENCES OF *P-R* INTERVALS OF HOSPITAL CONTROL SUBGROUPS AND TOTAL SERIES WITH VALUE IN TERMS OF THE PROBABLE ERROR.

Subgroup.	Subgroup Total Series	Difference.	X P E.
<i>Male.</i>			
Age 10-19		-0.87	-4.83 (Significant)
Age 20-29		-0.36	-1.89
Age 30-39		-0.07	-0.41
Age 40-49		+0.30	+1.67
Age 50-59		+0.68	+4.25 (Significant)
Age 60-69		+0.05	+0.31
<i>Female.</i>			
Age 10-19		-0.76	-4.75 (Significant)
Age 20-29		-0.41	-2.59
Age 30-39		+0.48	+2.82
Age 40-49		+0.22	+1.38
Age 50-59		+0.11	+0.65
Age 60-69		+0.78	+3.90 (Significant)

TABLE 9.—DIFFERENCES OF PULSE RATES OF HOSPITAL CONTROL SUBGROUPS AND TOTAL SERIES WITH VALUE IN TERMS OF THE PROBABLE ERROR.

Subgroup.	Subgroup Total Series	Difference.	X P E.
<i>Male.</i>			
Age 10-19		+2.65	+2.01
Age 20-29		-2.15	-1.52
Age 30-39		+0.60	+0.47
Age 40-49		-2.05	-1.55
Age 50-59		-0.15	-0.13
Age 60-69		+0.55	+0.48
<i>Female.</i>			
Age 10-19		+4.10	+4.06 (Significant)
Age 20-29		-0.65	-0.65
Age 30-39		+0.95	+0.90
Age 40-49		-3.40	-3.27 (Significant)
Age 50-59		+1.30	+1.18
Age 60-69		-3.30	-2.58

TABLE 10.—MEANS OF HOSPITAL MALES OF GROUPED AGES, 20-59 AND 30-59, USED FOR COMPARISON WITH ULCER AND GALL-BLADDER MALES OF SIMILAR GROUPED AGES.

Group.	Age in years.	No. of cases.	Range.	Mean and P E.	S D and P E.	V and P E.
<i>P-R Interval.</i>						
Hosp.	20-59	169	12-20	15.84 ± 0.08	1.65 ± 0.06	10.42 ± 0.38
Hosp.	30-59	134	12-20	15.98 ± 0.09	1.55 ± 0.06	9.70 ± 0.40
<i>Q-T Interval.</i>						
Hosp.	20-59	169	29-45	34.86 ± 0.14	2.70 ± 0.10	7.74 ± 0.28
Hosp.	30-59	134	29-45	34.95 ± 0.15	2.66 ± 0.11	7.61 ± 0.31
<i>Pulse Rate.</i>						
Hosp.	20-59	169	50-100	76.60 ± 0.64	12.30 ± 0.45	16.06 ± 0.59
Hosp.	30-59	134	50-100	76.94 ± 0.73	12.60 ± 0.52	16.38 ± 0.67

Comment. The significance of these findings is not clear, especially with regard to the prolonged *Q-T* interval found among gall-bladder folk. We shall investigate this point further. So far as the marked prolongation of the *P-R* interval in the ulcer group is

* Though not specifically referred to in the text, Tables 8, 9 and 10 are published in order to present the complete statistical analysis.

concerned, we have supposed that like the sinus arrhythmia and slow pulse rate it expresses a strong vagus influence. Supporting this notion is the recent work of Bruenn,¹ showing that the prolonged conduction time in acute rheumatic fever is almost wholly due to vagus effect. This prolongation, he found, could be abolished either by atropine or under the stress of emotional excitement.

In this connection attention should be called to the highly nervous state in which ulcer patients who are bleeding or in great pain enter the hospital, and indeed, to the swift energetic responses they make to life in general. Pulse rates observed on admission are invariably high. Only after the initial storm is over, and when the patient is free from pain and his blood and confidence restored, does the pulse rate fall to its own constitutional level. This process requires about 3 weeks.

We desire however to make quite clear that we do not conceive of these electrocardiographic findings as expressing a secondary effect of the ulcer. Rather do we regard the slow pulse, sinus arrhythmia and prolonged *P-R* interval as correlates of the ulcer and, like it, possibly indicating the peculiar vagotonicity of the ulcer subject. And here there seems perhaps to be a paradox. For it is well known that ulcer people often show wide palpebral fissures, easily sweating palms, rapid heart rate and general nervousness. We are inclined to believe however that the whole autonomic nervous system in people of ulcer constitution is high tension and labile, but that there is a special emphasis upon the parasympathetic division. Thus when fear, or the need of security suddenly impinges upon the consciousness of such a person the whole autonomic mechanism goes violently into action. Immediate effects of sympathetic stimulation appear—such as widened palpebral fissure, sweating, rapid pulse. But then there supervenes an equally strong and more prolonged vagus activity. This not only outlasts the sympathetic effects but may indeed specifically express the peculiar constitution of ulcer people.

There has been increasing support for the notion that the vagus nerve has much to do with ulcer production. The literature on the subject, which is very extensive, has been recently thoroughly digested in Cushing's³ monograph. But we are not at the moment so much concerned with the final cause of ulcer. Our interest is rather in trying to show that as total organisms the peptic ulcer susceptible person and the gall-bladder susceptible person are widely different from one another. These differences appear both in the morphologic and physiologic panels. It is possible to show that in each type a high correlation exists between body form, the pattern by which cardiac electropotential develops and disease proclivity. In addition to these findings, however, it appears that a technique which has heretofore been used in the clinic to detect pathologic

changes in function may also be employed to demonstrate special qualities of constitution.

Conclusions. A precision method has been used to study a constitutional character in the physiologic panel.

There is a high degree of constancy over long periods of time in the individual electrocardiographic pattern demonstrated in one or both of: (a) an unchanging pathologic state (Einthoven); and (b) the circumstance of a continually normal heart.

Significant differences between the electrocardiographic curve patterns for ulcer and gall-bladder people appear to exist within certain age groups.

These differences are also significantly distinct from the electrocardiograms of individuals with normal records selected from a general hospital population.

REFERENCES.

- (1.) Bruenn, H. G.: *Am. Heart J.*, 13, 413, 1937. (2.) Cohn, A. E., and Swift, H. F.: *J. Exp. Med.*, 39, 1, 1924. (3.) Cushing, H.: *Papers Relating to the Pituitary Body: Hypothalamus and Parasympathetic Nervous System; Peptic Ulcer and the Interbrain*, Springfield, Ill., Charles C Thomas, p. 175, 1932. (4.) Einthoven, W.: *Svenska Lak.-Sällsk. Handl.*, 51, 213, 1925. (5.) Laignel-Levastine, M., and Maingot, G.: *Bull. de l'Acad. de méd.*, series iii, 86, 228, 1921. (6.) Nielsen, J. M., and Roth, P.: *Arch. Int. Med.*, 43, 132, 1929.

ACTION OF THE DIAPHRAGM IN COUGH.

EXPERIMENTAL AND CLINICAL STUDY ON THE HUMAN.*

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THE action of the diaphragm in cough, sneezing, singing, laughing and similar "expiratory phenomena," has never been clearly determined. This problem has become of more clinical importance since phrenicectomy has been applied routinely in the treatment of pulmonary tuberculosis. Thus its solution has acquired considerable practical significance.

Recent experimental and clinical investigations have modified the ideas of the clinician on cough. Cough is no longer the troublesome and annoying symptom requiring alleviation, but a phenomenon which plays an important part in the pathogenesis and the course of pulmonary diseases and when skillfully directed may be of

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great help in their treatment. Bronchial retention and obstruction, which thus far have been given insufficient consideration, are now known to be the principal factors in the pathogenesis of various morbid syndromes of the lung. In atelectasis, postoperative and medical pneumonia, abscess of the lung, bronchiectasis and other pathologic states, bronchial obstruction plays an important rôle in the production and the course of the disease. In fact, when the patency of the bronchi is hampered or suppressed, the part of the lung dependent upon the obstructed bronchus is not only functionally suppressed, but also the fate of its parenchyma will depend upon the nature and the toxicity of microorganisms which may be present in the obstructing agent. While sterile foreign bodies produce, as a rule, uncomplicated atelectasis, septic material coming from the upper respiratory ways may cause suppurative pneumonitis, gangrene or putrid abscess of the lung. Obstruction of a lobar bronchus by viscid and tenacious pneumococcic bronchial exudate may cause, according to the virulence of pneumococcus present in it, benign pneumococcic atelectasis or toxic pneumonia, postoperative or medical.^{7a, 8b, c}

The serious effects of defective bronchial drainage are especially appreciated by the surgeon and more particularly by the thoracic surgeon. We all have learned to dread this complication in patients with pulmonary suppurations. In thoracoplasties for pulmonary tuberculosis or lobectomies for bronchiectasis, bronchial retention represents the most important single factor in the pathogenesis of all postoperative hemo-respiratory and toxic complications.^{7b} Many such patients have been saved from impending asphyxial death by immediate bronchial aspiration and many patients with pulmonary tuberculosis or putrid abscesses have died because of unrecognized retention in the bronchi of the infected exudate. The term "septic bronchial embolism," coined by Ameuille,¹ gives an accurate idea of the pathogenesis of these complications.

Against bronchial retention and obstruction the lung utilizes several and powerful means of defense; this organ, like the intestine, being especially exposed to infection, requires perfect drainage. Of these means of defense, cough is the most important; it is the "watch dog" of the lung as Jackson has put it.¹² Its suppression paralyzes the whole system of defense, since the full action of the ciliary epithelium and of the peristaltic movements of the bronchi are greatly handicapped or suppressed.

Charts of patients with acute or chronic pulmonary infections in which temperatures and amounts of sputum are recorded are most instructive; when cough is hampered and the amount of expectoration decreases, temperature rises and toxicity increases. Conversely, when cough and expectoration are reestablished, temperature drops and the condition rapidly improves.^{7b} It is well known that a few coughing spells usually clear up all symptoms of postoperative

atelectasis and have prevented many asphyxias following hemoptysis in tuberculous patients.

These new conceptions have increased the need of more positive knowledge on the action of the diaphragm in cough. Thus far, no satisfactory solution of this problem has been presented either by physiologists or clinicians. The confusion prevailing in our concept on this subject was clearly shown in an editorial comment⁹ on diaphragm in cough: "In all acts of expulsion, coughing, sneezing, laughing, vomiting and crying the diaphragm adds force to the expulsive effort." A reader, Dr. W. D. Zoethout,¹⁰ surprised by this statement, addressed a letter to the editor asking him if he would "kindly explain how the musculature of the diaphragm can contribute power to expiratory efforts."¹⁰ The editor, in his answer, reversed his previous statement and wrote: "There is at present no evidence that the diaphragm adds power to these processes (coughing, sneezing, laughing, crying), which are expiratory acts, or that it favors the expulsion of air out of the lungs. . . ."

Going over the clinical papers related to phrenic interruption in the human, we find the same quandary. A number of authors believe that paralysis of the diaphragm "renders expulsion of sputum easier," others that it "decreases expectoration," and others that "it is without any noticeable effect upon cough and expectoration." An excellent analysis of these conflicting opinions was presented by Carlson, Ballou, Wilson and Graham.⁴ Thus Wall¹⁷ attributed the improvement occasionally following phrenicectomy for bronchiectasis to "the greater ease of expectoration which prevents stagnation and decomposition of the exudate in the dilated bronchial tubes." Straub believed that expectoration was facilitated after phrenicectomy because of "the greater compression exerted upon the lungs by the contraction of the abdominal muscles with the diaphragm flaccid." On the contrary, Cooper⁶ found that cough was decreased in 40% of these cases. Chernyk⁵ came to the conclusion that the effect of phrenicectomy upon cough and expectoration in pulmonary tuberculosis was either favorable or unfavorable, regardless of whether the lesion was located in the base or the apex. The same opinion was expressed by Moore.¹⁴ Wilson,¹⁸ in 21 cases of pulmonary tuberculosis, found that after phrenicectomy expectoration was easier in 5, more difficult in 3 and remained unchanged in 12. Likewise in 18 cases of bronchiectasis, expectoration was made easier in 4, more difficult in 3 and remained unchanged in 11. Berry,³ in his paper on the results of phrenicectomy, concluded that "in numerous cases paralysis of the diaphragm so hindered cough and drainage that the secretions puddled in the lung and extensive pneumonia developed."

Experimental investigation on animals upon the effects of diaphragmatic paralysis on cough has also led to conflicting conclusions. Lemon¹³ and Coryllos and Birnbaum^{8a} have noticed no

changes in the respiratory capacity of the dog following phrenicectomy, unilateral or even bilateral. Fine and Starr,¹¹ in a recent paper, concluded that, in the dog, "paralysis of the diaphragm affords neither help nor hindrance to the force of the expiratory blast, . . . If cough is somewhat less efficient it must be related to other factors such as less inspiratory expansion of the lungs with consequent decrease in the air available for the expiratory blast."

On the contrary, Carlson⁴ and his collaborators, have found that lipiodol or foreign bodies (birdshot) introduced into the bronchi of the dog were eliminated more rapidly from the lung with healthy diaphragm than from the lung with paralyzed diaphragm. In one of their experiments, lipiodol was emptied from the lung of the side of the intact diaphragm within 14 days, whereas it remained 59 days in the lung with the paralyzed diaphragm; following phrenicectomy of the intact side, on the same animal, lipiodol was still present in both lungs 30 days later, when the animal died. They concluded that the elimination of lipiodol and foreign bodies is retarded after paralysis of the diaphragm and that at any rate no evidence was found to support the contention that cough and expectoration are facilitated by interruption of the phrenic nerve.

This short review of clinical and experimental data shows that our present knowledge on the action of the diaphragm in cough and expectoration is very limited; we are even in doubt whether there is any such action. Because of these discrepancies, we decided to investigate further this interesting problem.

It soon, however, became clear to us that no progress could be made without more precise knowledge of the mechanics of cough: for if cough really were a purely expiratory phenomenon, the diaphragm, being a strictly inspiratory muscle, should not have any action upon it. But, is cough an exclusively expiratory act? There are in the literature a few statements which were apparently made casually without any particular importance attached. Carlson *et al.*⁴ said (loc. cit., p. 575): "As each cough is usually preceded or followed by a deep inspiration and as the diaphragm is an important muscle of inspiration it is probable that in a succession of coughs the excursion of the diaphragm will in some measure condition the efficiency of cough. . . ." On the other hand, Archibald and Brown² wrote in their experimental study of cough: "The contraction of the abdominal muscles increases the abdominal pressure which is transmitted through the *semirigid diaphragm* into the thoracic cage," and "while the intercostal muscles tend to elongate the bony framework of the thorax and thus decrease its capacity, the accompanying *contraction and fixation* of the diaphragm further narrow the chest cavity. . . ."

These two ideas of "conditioning of cough," and of possible "contraction of the diaphragm during cough" were the starting points of this work. They furnished a working hypothesis and

aroused doubt as to the solidity of the conception that cough was a strictly expiratory act. In fact, as our work progressed, we were forced to reject this generally accepted opinion. We gradually came to formulate a new theory which seems more in agreement with clinical and experimental data; and throws, we believe, a new light on the relation of diaphragm to cough.

Mechanics of Cough. Our study was based upon the fact that in the presence of a moderate pneumothorax without fluid and with normal parietal and visceral pleuræ, any changes occurring in the intrapulmonary pressures are integrally transmitted to the pleural air, since variations of intrapulmonary pressures occurring during cough are due to the changes of the capacity of the thorax. It is obvious that they must be registered accurately in the graph recorded by a manometer connected with the pleural cavity.

The great number of patients with pneumothorax and phrenicectomy treated in our services offered us the opportunity of comparative studies of intrapleural pressures during cough with intact and with paralyzed diaphragm on the human. Furthermore, patients having bilateral pneumothorax and unilateral paralysis of the diaphragm rendered possible the study of the action of the diaphragm in cough with and without paralysis of the diaphragm on the same patient. We are indebted to our patients for their kind coöperation in this investigation.

Technique. With all usual aseptic precautions, and at the time of a refill for pneumothorax, the needle introduced into the pleural cavity was connected, by means of an aseptic rubber tube, with a recording chloroform manometer. This worked better than the water manometer and gave satisfactory excursions for our records.

This mode of investigation offered a number of marked advantages. It not only permitted the recording of fine changes of pressures occurring during cough in the human, but it also rendered possible the avoidance of errors inherent in experimentation on animals, especially the dog. In fact, if animals are studied, they should be anesthetized and cough produced by artificial stimulation of the larynx. Moreover, the mediastinum of the dog, represented by a flimsy membrane readily permeable to gases, cannot be compared to the thick and more resistant human mediastinum. Furthermore, the horizontal position in which the animal should remain during the experiment does influence the action of the heavy abdominal viscera upon the diaphragm.

Another point of importance is that in the human, the strength, rhythm and frequency of cough can be made to vary at will, thus allowing investigation of this phenomenon in all its details. Last but not least, this procedure renders possible the study of cough in its relations to pathologic conditions of the lung, of the pleura and of the chest walls, which is impossible in animals. Study of cough in consolidation of the lung, bronchial stenosis or obstruction,

fibrotic or atelectatic retraction of the lung, in decreased pulmonary expansion due to thickened visceral pleura, in rigid mediastinum, in the presence of fluid in the pleural cavity and in reduced mobility of the chest walls following thoracoplasty or excessive inflammatory thickening of the parietal pleura, are of considerable interest.

It is not our intention to enter here into these details which will be reported later. We shall limit this study to the mechanics of cough in cases with normal or almost normal lungs, pleura and chest wall.

Our Concept. We regard cough as far from a simple expiratory phenomenon. It really is composed of three distinct phases, inspiratory, compressive and expulsive, each of which presents special mechanical and physiologic characteristics. Cough is represented by the integration of these three phases; none of them can be omitted when we consider cough, without exposure to misinterpretations and erroneous conclusions. In other words, cough should be considered as a whole; it is a reflex phenomenon which can be started and stopped voluntarily. However, once started, and if not interfered with, it proceeds according to a fixed pattern, just as do deglutition, vomiting and defecation.

Cough is composed of a deep inspiration followed by a strong expiration. However, the expiratory act is in reality composed of two different phases: one, short, during which the glottis remains closed and strong positive pressure is built up in the lungs; the second is longer, begins with the opening of the glottis and ends with the sustained expulsion of the compressed air.

Thus cough is composed of three distinct phases: "Inspiratory," "compressive" and "expulsive." These three phases can be likened to the three phases of the deflagration of a gun; the inspiratory to the loading of the gun, the compressive phase to the deflagration of powder and production of gases under pressure, and the expulsive phase to the ejection of the bullet from the barrel of the gun.

This partition of cough into three phases facilitates the study of the action of the diaphragm separately in each.

1. *Inspiratory Phase.* During the inspiratory phase, the action of the diaphragm is evident. It is also obvious that the amount of air loaded into the corresponding lung depends upon the condition of the diaphragm. When this muscle is paralyzed it cannot contract and therefore the vertical diameter of the chest is not increased. Hence, the capacity of the hemithorax corresponding to the paralyzed diaphragm increases less than that of the other side. Furthermore, as after phrenicectomy the diaphragm loses its tonus and elasticity and is changed to a flimsy membrane, it is drawn upward during inspiratory increase of the intrapleural negative pressure. It should be noted, however, that because of the normal contraction of the healthy diaphragm the inspiratory negative pressure is greater in the healthy side; therefore the mediastinum

is displaced towards this side and thus the difference between the pressures of the two hemithoraces tends to decrease. Nevertheless, complete equilibrium can be reached only in animals with an extremely mobile mediastinum, such as the dog. Therefore with the hemiparalyzed diaphragm of man the amount of air is smaller and the expiratory blast of air during the third phase less strong.

Much more than by hemiparalysis is the inspiratory phase of cough influenced by any cause which impairs the ability of the lung to expand; bronchial obstruction of any kind, the presence of large amounts of fluid in the pleural cavity, thickening of the parietal and visceral pleuræ or immobilization of the chest wall to expand (chronic empyema, thoracoplasty)—all these diminish considerably the efficiency of this phase of cough.

2. *Compressive Phase.* During the second or compressive phase the action of the diaphragm is of the greatest interest. In fact, high positive pressures cannot be built up in the chest unless its walls have acquired a rigidity proportionate to these pressures. Therefore, the rigidity must be considerable since the positive pressures reach 80 and even 100 mm. Hg.

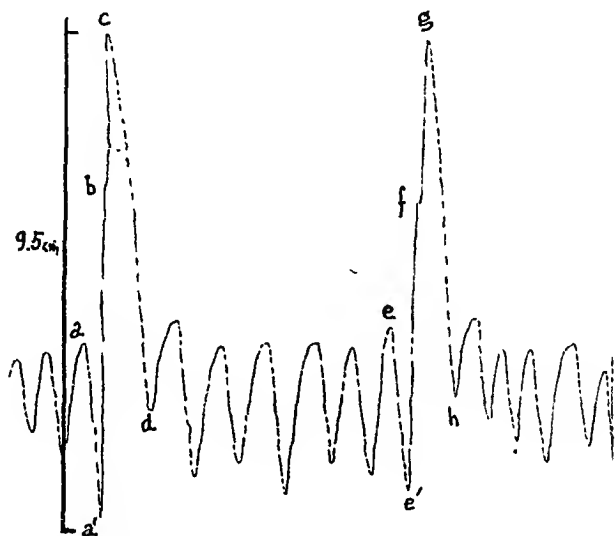
Let us follow this phase closely. Under the action of the expiratory muscles, the most important of which are the abdominal muscles, the ribs and sternum are drawn downwards causing a marked reduction of the capacity of the chest and pressure upon the air which is entrapped into the lung by the closure of the glottis. It should always be remembered that positive pressures in the chest are due to the centripetal compression exerted upon the inflated lungs by the retracting chest walls and the compressed abdominal viscera.

It is easy to understand the mechanism by which the rigidity of the thoracic walls is insured. The bony skeleton of its walls, complemented by the contracting intercostal muscles, can easily transform the thorax into a rigid cage. But there are the upper and the lower openings of the chest. The superior opening is small and the apical pleuræ which obturate it superiorly are solidly reinforced by numerous fibrotic bands; in the center we find an extrapleural space occupied by the organs passing from the neck into the chest.

It is more difficult to understand the mechanism by which the soft and easily yielding diaphragm, representing the bottom of the thoracic cage, acquires the considerable rigidity necessary to resist such enormous positive pressures as 80 to 100 mm. Hg, or even more. Three hypotheses are possible.

A. That the propulsion of the abdominal viscera upwards under the action of the contracting abdominal muscles is checked by the tonus and the elasticity of the diaphragm. But this cannot be true, because then the diaphragm should be strained to its breaking point and should not rise further into the chest in each successive cough movement.

B. The push of the abdominal viscera comes to an equilibrium with the increased intrathoracic pressure. Thus the subsequent rising of the diaphragm with each cough could be explained by the decreased intrathoracic pressure following each short opening of the glottis. But if this were so, why does the paralyzed diaphragm rise into the chest far above the healthy one; moreover why, at each opening of the glottis, does it jump much higher than the non-paralyzed one? In fact, when we follow in the fluoroscope the movements of the diaphragm of a patient with the diaphragm



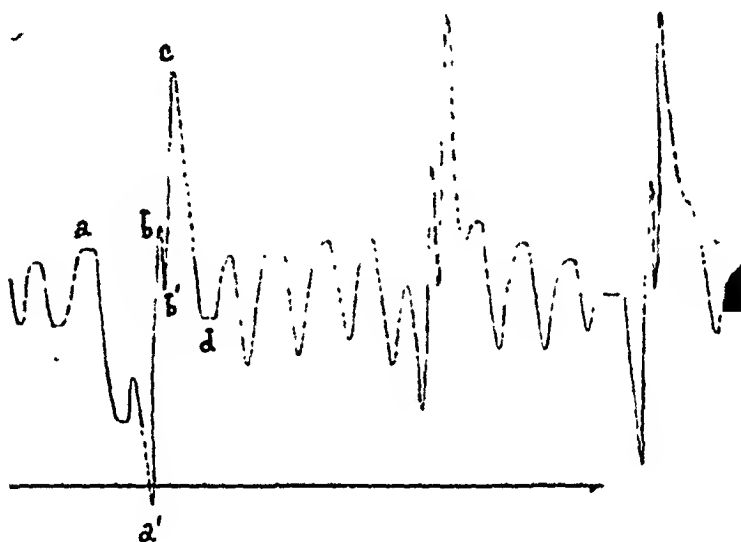
GRAPH 1.—Patient T. G., aged 23, female, pulmonary tuberculosis. Pneumothorax. Diaphragms intact. Graphs of two cough movements without inspiratory interruption, inspiration downstroke.

paralyzed on one side, while the patient is instructed to make short successive coughs without inspiratory movement between them, we see very clearly that the healthy diaphragm rises a little more with each cough, whereas the paralyzed diaphragm "jumps" high and falls again. We must admit, therefore, that something holds down the viscera during the opening of the glottis and that this cannot be the tonus alone of the diaphragm. The unquestionable conclusion is that the diaphragm does contract during the compressive phase of cough.

C. The third hypothesis is that the diaphragm contracts during the compressive and the expulsive phases of cough. Thus the diaphragm checks the rise of the viscera into the chest and renders rigid the bottom of the thoracic cavity. It will be shown that this concept offers an easy explanation of other puzzling questions concerning the expulsive phase of cough.

These differences in the movements of the healthy and paralyzed diaphragms are clearly shown in our graphs. We give here two of them. These graphs were obtained by a recording chloroform manometer connected by a rubber tube to the usual pneumothorax needle introduced into pleural cavities with healthy (Graph 1) and with paralyzed diaphragm (Graph 2).

Following are clinical notes of the 2 patients who furnished these graphs and who were selected as nearly similar as possible.



GRAPH 2.—Patient F. L., aged 22, female. Pulmonary tuberculosis. Right pneumothorax and previous avulsion of the right phrenic nerve. Right diaphragm paralyzed, inspiration downstroke.

CASE 1.—T. G., aged 23, female, Puerto Rican; bilateral pulmonary tuberculosis; had had bilateral pneumothorax, completed by bilateral pneumonolysis. Both upper lobes were selectively collapsed while the lower lobes of both lungs were allowed to reëxpand. The vital capacity was 1200 cc. The phrenic nerves were intact and the function of the diaphragm was normal.

CASE 2.—F. L., aged 22, white, had a pneumothorax in one side. A complete avulsion of the phrenic nerve (30 cm.) had been performed previously. Pneumonolysis was performed for section of apical adhesions which had opposed a selective collapse of the apex. Actually the upper lobe was selectively collapsed while the lower lobe was allowed to reëxpand. Vital capacity, 1400 cc.

Since all other conditions in these patients were identical, it seems reasonable to assume that all differences shown in the two records should be ascribed to the paralysis of the diaphragm.

These patients were instructed to cough twice in succession without inspiratory interruption, so that each graph would represent two movements of cough without intervening inspiration.

For reasons developed previously, it can be accepted that the changes in pressures in the pleura faithfully translate corresponding changes of pressures in the lung, so that in the last analysis it makes no difference whether the graphs were taken from the pleura or directly from the lung—the latter being impossible in the human. A study of the two graphs shows that they differ in all three phases but more especially in the compressive and expulsive ones.

In Graph 1, the inspiratory phase (aa') is represented by a clean-cut downstroke, about three times longer than the downstroke of the normal quiet inspiration. It is accomplished in two movements (aa'); it is possible that the first downstroke is due to the expansion of the chest and the second to the contraction of the healthy diaphragm of the other side, causing as was said above, displacement of the mediastinum towards the healthy side. Moreover it has been repeatedly, although not constantly, noted that the inspiratory movement preceding cough starts a trifle earlier in the thorax with paralyzed diaphragm than on the healthy side.

The upstroke $a'bc$ presents the compressive phase of two successive cough movements $a'b$ in the first and Cc in the second. C marks (Graph 1) the short period between the two coughs during which the glottis was opened. It is clearly shown that this short and partial release of pressure affects very little the intrapleural and intrapulmonary pressures on the side with healthy diaphragm.

In Graph 2 we find that the two cough movements $a'b$ and $b'c$ are separated by a downstroke bb' ; this indicates either that during the short opening of the glottis a more marked drop of pressure occurred on this side or that the push of the viscera upwards at the end of the first cough was not checked as in Case 1. Obviously, a more marked drop of intrapleural (and intrapulmonary) pressures on the side of the paralyzed diaphragm is not admissible because this drop, due to the opening of the glottis, is independent of the condition of the diaphragm.

3. *Expulsive Phase.* In the third, or expulsive, phase of cough, this checking action of the diaphragm becomes more apparent. If we inspect the abdomen of a man during cough, we see that in each coughing effort a movement of retraction of the abdominal wall takes place. When a subject is instructed to perform successive movements of cough without inspiratory interruption, we see successive contractions of the abdominal walls so that they retract each time a little more than in the preceding movement. When a subject with healthy diaphragm is examined fluoroscopically while coughing, the diaphragm is seen to assume a little more elevated position with each cough. It seems to restrain the abdominal viscera from jumping upwards into the chest cavity, as occurs when the diaphragm is paralyzed. This is particularly noticeable when a subject makes strong successive cough movements in an endeavor to expel tenacious sputum. In each movement the diaphragm rises a little more,

as if it were regulating the expulsion of air in an effort to prevent waste of time, air and energy. Likewise, the diaphragm acting as an antagonist to the abdominal muscles, regulates the strength and length of cough to the needs, that is, to the resistance opposed by foreign bodies present in the bronchial tree. There is no doubt that this adjustment is necessary and does take place. We do not cough with the same strength when we strive to dislodge tenacious sputum or a foreign body stuck to the bronchi as when we gently push a small quantity of phlegm from the upper respiratory ways.

At the same time, by its synchronous contraction with the abdominal muscles, the diaphragm insures the rigidity of the floor of the thorax during the compressive and expulsive phases of cough. This is a prerequisite condition because of the tremendous positive pressures necessary for the production of the strong draft of air needed for the expulsion of foreign matter from the bronchial tree. Rohrer¹⁵ has calculated the velocity of air during cough as it passes through the various segments of the human respiratory tract. He found that it varied from 0.5 to 2 meters per second in the respiratory bronchioli and from 50 to 120 meters (150 to 360 feet) per second in the glottis. These latter velocities are comparable to wind velocities of severe storms. Calculated at 300 feet per second, the speed of air in the glottis is equal to 20 miles an hour, which compares very favorably with the 30 mile per hour wind speed of strong hurricanes.

Comment. The facts thus far shown in this study seem to prove that the diaphragm contracts during the three phases of cough. If this contention is accepted, the explanation of all difficult points on cough become simple.

The rigidity of the floor of the chest, unaccounted for in other theories, a condition necessary for the development of high positive pressures in the lungs during the compressive period of cough, is easily explained. The pushing upwards of the abdominal viscera against the downward pushing of the contracting diaphragm insures the rigidity of the bottom of the thorax in the same way as the simultaneous contraction of flexor and extensor muscles of the arm and forearm insures the rigidity of the elbow. In fact, this is the usual mechanism by which rigidity is obtained in any part of the body.

Thus, the diaphragm here acts as a muscle antagonist to the abdominal and other expiratory muscles. This conclusion is, I believe, the most important point and gives us the key to the whole problem of the action of the diaphragm in cough. It is a simple physiologic law that wherever in the organism a movement is accomplished either by the skeletal or visceral muscles, it is always performed by the co-action of two antagonist muscular systems—one acting as a brake upon the other. It is by this mechanism that movements can be adjusted to the needs with accuracy and without waste of

time and energy. We know that the accuracy and speed of movements of the fingers is hampered when the integrity of either their flexor or extensor system is disturbed. Likewise the regularity and efficiency of movements of the intestine are disturbed when either their sympathetic or their vagus innervation is involved. This fine co-action of the two antagonist muscular systems is seen also in all tubular organs, such as the esophagus, ureters, and so forth; when a foreign body is present in their lumen, peristaltic contractions of their walls tend to expel the obstructing agent; the strength of these movements is adjusted to the resistance offered by the foreign body.

The same mechanism is repeated in cough. The objective of the reflex is the expulsion of foreign matter lodged in the bronchi; the means to this effect are blasts of air, besides the "tussic squeeze" of Jackson¹²; it is obvious that the strength and rhythm of these blasts must be proportionate to the resistance offered by these agents. Therefore, a regulating mechanism of the blasts of air is necessary in order to adjust their expelling strength without waste of the explosive material—here the compressed air—and of energy, represented here by the action of the muscles activating the bellows. Therefore, the theory of the co-action of two antagonistic motor systems can alone explain the regulating mechanism of cough.

This action of the diaphragm is well seen and easily proven in other expiratory acts, similar to cough but less rapid and less explosive than cough, or sneezing. Such acts are singing and effort; when we observe in the fluoroscope a person while he sings, whistles or emits a continuous sound we can clearly see this regulating action of the diaphragm. Likewise during manual effort, in which the chest is immobilized in inspiration with the glottis closed in order to insure a steady point of insertion for the muscles of the arms and of the abdomen, again the degree of contraction of the diaphragm and of the abdominal muscles are proportionate to the positive pressures which should be built up in the chest in order to insure an immobilization and rigidity of the chest cage proportionate to the effort. We do not find the same intrathoracic pressures when a man tries to lift 50 pounds as when he tries to lift 500 pounds.

Thus the diaphragm, contrary to the theories accepted thus far that "it is without any action in coughing, sneezing, crying, etc.," does take an important part in all expiratory acts such as cough, sneezing, singing, effort, and so forth. However, the diaphragm does not directly help expulsion of air from the lungs. The action of this muscle is *to regulate and adjust the expulsive efficiency of cough*. This action is one more example of the amazing efficiency, accuracy and economy with which the body machine operates.

Conclusions. 1. Review of knowledge of the action of the diaphragm in cough reveals the absence of any acceptable concept on this subject.

2. Clinical and experimental evidence suggest a new conception,

according to which the action of the diaphragm is that of a regulator of the strength of the expulsive force of cough necessary to overcome the resistance of matter lodged in the bronchial tree.

3. Cough is not a simple expiratory act but is composed of three distinct phases, inspiratory, compressive and expulsive.

4. The diaphragm acts as an antagonist muscle to the expiratory muscles and contracts during the three phases of cough; by its co-action with its antagonist expiratory, thoracic and abdominal muscles, it insures the rigidity of the floor of the thoracic cage during its compressive phase and it regulates the efficiency of cough with the greatest saving of time and energy during its expulsive phase. This action of the diaphragm is in accordance with the general physiologic laws of movement in the animal economy.

REFERENCES.

- (1.) Ameuille, P.: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 48, 791, 1924. (2.) Archibald, E., and Brown, A. L.: *Arch. Surg.*, 16, 322, 1928. (3.) Berry, F. B.: *Ibid.*, 21, 1125, 1930. (4.) Carlson, H. A., Ballou, H. C., Wilson, H. M., and Graham, E. A.: *J. Thorac. Surg.*, 2, 573, 1933. (5.) Chernyk: Quoted in Carlson Ref. 10. (6.) Cooper, A. T.: *Am. Rev. Tuberc.*, 22, 769, 1930. (7.) Coryllos, P. N.: (a) *Surg., Gynec. and Obst.*, 50, 795, 1930; (b) *J. Thorac. Surg.*, 2, 354, 1934. (8.) Coryllos, P. N., and Birnbaum, G. L.: (a) *Arch. Surg.*, 16, 501, 1928; (b) *Am. J. Roent.*, 22, 401, 1929; (c) *Arch. Int. Med.*, 51, 290, 1933. (9.) Editorial: *J. Am. Med. Assn.*, 91, 1894, 1928. (10.) Editorial: *Ibid.*, 92, 496, 1928. (11.) Fine, J., and Starr, A.: *J. Thorac. Surg.*, 4, 525, 1934-1935. (12.) Jackson, C., and Jackson, C. L.: *Am. J. Med. Sci.*, 186, 849, 1933. (13.) Lemon, W. S.: *Arch. Surg.*, 14, 345, 1927. (14.) Moore, A. J.: *Ibid.*, 20, 175, 1930. (15.) Rohrer, F.: *Schweiz. med. Wehnschr.*, 2, 765, 1921. (16.) Straub, G. F.: *Surgery of the Chest*, Springfield, Ill., Charles C Thomas, 1932. (17.) Wall, C.: *Lancet*, 2, 957, 1928. (18.) Wilson, H.: *Med. J. Australia*, 2, 487, 1930.

CARCINOMA OF THE BRONCHUS IN ASSOCIATION WITH ANTHRACOSILICOSIS.

A STUDY OF FOUR CASES.

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IN a condition such as anthracosilicosis in which chronic irritation of the bronchus and lung by coal and silica is an outstanding feature, a relatively high incidence of primary bronchial and pulmonary carcinoma might be expected. From postmortem findings, however, it has been generally regarded that there is no relationship between pneumoconiosis and pulmonary new growths. In fact, only a few cases of bronchogenic carcinoma in association with anthracosilicosis are reported.^{1,4,5}

Between January, 1934, and December, 1936, 174 cases of anthracosilicosis in various stages, with or without pulmonary tubercu-

losis, were treated at this Sanatorium. Of this number, 36 came to necropsy. Among these, 4 presented primary carcinoma of the bronchus. Briefly, the clinical and pathologic observations on these cases are as follows:

Case Abstracts.—**CASE 1** (No. 9199). White male, aged 43, anthracite coal miner 9 years, was admitted on March 3, 1934, complaining of dyspnea, hemoptysis, pain in the left chest, cough and expectoration. He had noted dyspnea on exertion 4 months previously, soon followed by persistent dull pain in the left chest. A dry cough developed which later became productive. The sputum was constantly mixed with blood. The family history was negative and there was no past history of influenza.

Physical Examination. Chest was rounded, expansion and vocal fremitus equal on both sides. There was slight dullness over the left apex but resonance over the rest of the left lung and the entire right lung. The breath sounds were loud over both lungs, including the left apex. No râles. The sputum was negative for tubercle bacilli in 26 specimens.

Röntgen Ray Examination (Fig. 1) showed a homogeneous opacity involving the left upper lobe area with scattered mottling throughout the remainder of the left lung and the entire right lung.

Temperature was normal except on two occasions when it rose to 101° F. Pulse rate varied from 90 to 100, and respiratory rate 25 to 30 per minute.

Dyspnea and cough became worse. The sputum was constantly mixed with large amounts of fresh blood. Pain in the left chest persisted. The patient died May 23, 1934.

Necropsy. A large tumor encircled the trachea and aorta. The left lung showed a hard tumor occluding the upper lobe bronchus and producing atelectasis of that lobe. In the center of the atelectatic lobe was a large cavity containing necrotic material. Throughout the left lung were scattered small tumor nodules. The hilum lymph nodes showed metastasis.

Microscopic Examination. The tumor consisted of small round and occasionally spindle-shaped cells with dark nuclei and scanty cytoplasm and considerable intercellular stroma. The anthracosilicotic nodules were extensively broken up. Some tumor cells formed glandlike structures. The bronchioles showed desquamation. The lymph channels were filled with tumor cells. Large necrotic areas were common and many of the tumor nodules showed central necrosis. The bronchial cartilages were extensively destroyed by tumor cells. Diagnosis: Carcinoma, undifferentiated type.

CASE 2 (No. 9477). White male, aged 48, anthracite coal miner 25 years, was admitted on July 6, 1935, complaining of dyspnea, hemoptysis, pain in the right chest, cough and expectoration. He had noted dyspnea on exertion for 4 months. About the same time he began to feel persistent pain in the right chest. Soon cough set in with expectoration of about 2 oz. of blood-streaked sputum daily. The family history was negative and there was no past history of influenza.

Physical Examination. Chest was rounded, expansion limited on the right side, with absent fremitus over the right lower chest where the percussion note was flat and the breath sounds were absent. The right upper lobe and the entire left lung were resonant and the breath sounds well heard. A few crackling râles were present over the left base. Heart was displaced to the left side. The sputum was negative for tubercle bacilli in 13 specimens.

Röntgen Ray Examination (Fig. 2) revealed a dense shadow in the right lower chest, suggesting pleural effusion. Throughout the remainder of the right lung and the entire left lung were prominent tissue markings and dis-



FIG.
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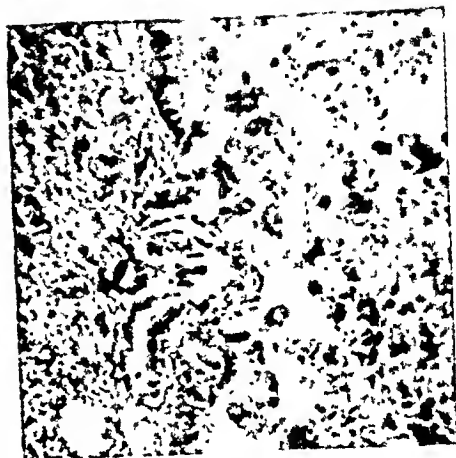


FIG.
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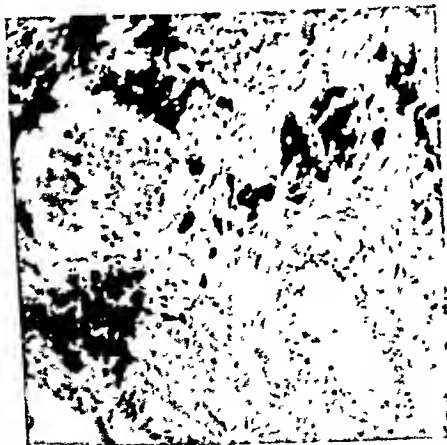


FIG.
6.

FIG. 1.—Atelectasis of left upper lobe due to bronchial obstruction. Nodules in remainder of left lung. Increased tissue markings in right lung.

FIG. 2.—Pleural effusion on the right. Increased tissue markings and disseminated nodules in both lungs.

FIG. 3.—Tumor cells passing through an alveolar pore. ($\times 450$.)

FIG. 4.—A tumor rupturing into a bronchus. ($\times 100$.)

FIG. 5.—Perivascular lymph vessels engorged with tumor cells. ($\times 100$.)

FIG. 6.—Tumor cells in an interlobar adhesion. ($\times 100$.)

FIG.
7.

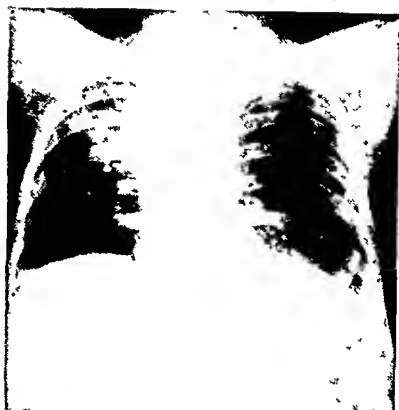
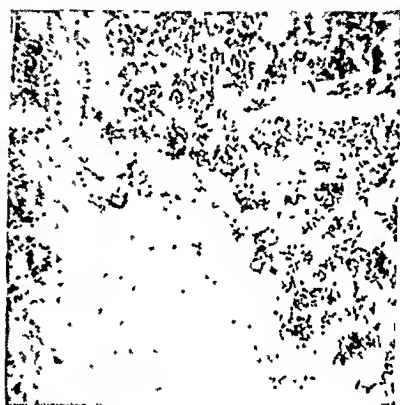
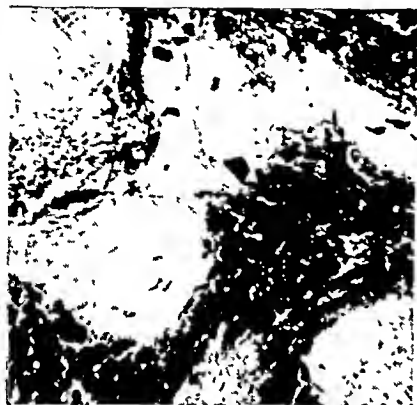


FIG.
8.



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FIG. 11.

FIG. 7.—Atelectasis of left lung due to bronchial obstruction. Nodules in right lung.

FIG. 8.—Invasion of anthracosilicotic nodule by tumor cells. ($\times 100$.)

FIG. 9.—Atelectasis of right upper lobe. Increased tissue markings in left lung and remainder of right lung.

FIG. 10.—Destruction of bronchial cartilage by tumor cells. ($\times 100$.)

FIG. 11.—Pulmonary artery in atelectatic right upper lobe has fewer ramifications, and its caliber is narrowed.

seminated small poorly defined nodular shadows, being most numerous in the hilum regions.

Temperature was practically normal. Pulse rate varied from 84 to 100, and respiratory rate between 20 to 35 per minute.

On August 20, 1935, the patient developed a complete left sided hemiplegia and died within an hour.

Necropsy. Directly beneath the visceral pleura of each lung were scattered grayish nodules varying in size from a pin-point to 1 mm. Intermingled with these were anthracosilicotic nodules measuring from 1 mm. to 5 mm. The visceral pleura of the right lung was thickened and covered with fibrinous material. Both kinds of nodules were prominent on section. There was considerable peribronchial and perivascular fibrosis. Some bronchioles were occluded with cell debris. Several small blood-vessels were thrombosed. The liver and kidneys showed grayish nodules of the same character as those in the lungs. Other organs in the abdomen and pelvis were negative.

Microscopic Examination. The grayish nodules were tumors consisting of cylindrical and cuboidal cells having pale nuclei, oval in shape. In many areas the alveolar septa were lined by tumor cells, some of which formed papillary projections into the alveolar spaces, while others were passing through the alveolar pores (Fig. 3). Anthracosilicotic nodules were broken up by tumor cells. The mucosa of the bronchioles showed thinning and areas of desquamation. Small tumors disrupted the bronchial mucosa and discharged the tumor cells into the bronchial lumen (Fig. 4). There was much peribronchial and perivascular fibrosis. The peribronchial and perivascular lymph channels were filled with tumor cells (Fig. 5). Thrombosed blood-vessels were most numerous in the right lower lobe and surrounding them were areas of infarction, some of which showed fibrotic capsules. The pleura over the right lung showed tumor cells covering its surface. The strandlike adhesions between the lower and middle lobes showed tumor cells (Fig. 6). The bronchial cartilages were extensively destroyed by tumor cells. Diagnosis: Cylindrical cell carcinoma.

CASE 3 (No. 9534). White male, aged 53, anthracite coal miner 43 years, was admitted on September 20, 1935, complaining of dyspnea, hemoptysis, cough and expectoration. The onset was 1½ years previous to admission when he noticed dyspnea on exertion, which gradually became worse. For the past 20 years he has had slight cough and expectoration which became worse during the last 2 months. Shortly before admission he had hemoptysis and thereafter the sputum was frequently blood-streaked. The family history was negative and there was no past history of influenza.

Physical Examination. Chest was rounded. There was limited expansion on the left with diminished vocal fremitus and dullness over the upper lobe. Over the rest of the left lung and the entire right lung was resonance with loud breath sounds. Heart was displaced to the left. The sputum was negative for tubercle bacilli in 7 specimens.

Röntgen Ray Examination (Fig. 7) showed numerous independent nodular shadows throughout the right lung. On the left was even density with displacement of the heart to that side.

Temperature was normal. Pulse rate was from 80 to 100, and respiratory rate from 25 to 35 per minute.

Following admission, dyspnea, cough and expectoration became worse and the patient died on October 6, 1935.

Necropsy. Both lungs showed scattered anthracosilicotic nodules measuring from 1 mm. to 5 mm. The left upper lobe was atelectatic due to an occlusion of its bronchus by a tumor. Within the center of the atelectatic lobe were four cavities containing necrotic material. The left lower lobe presented an appearance of gray hepatization. There was much peri-

bronchial and perivascular fibrosis in both lungs. Some blood-vessels were thrombosed.

Microscopic Examination. The tumor consisted of squamous cells showing pearl formation. Many tumor nodules showed necrotic centers. The lymph vessels contained tumor cells in large numbers. The blood-vessels were sclerotic with a great deal of perivascular fibrosis and some were thrombosed. Adjacent to the thrombotic vessels were areas of infarction, some of which had undergone necrosis. Some infarcts had fibrous capsules. Anthracosilicotic nodules were numerous and many of them were extensively broken up by tumor cells (Fig. 8). In the left lung, the alveolar septa were greatly thickened by increase of the connective tissue and cellular infiltration. The alveoli were filled with fibrinous material containing tumor cells. Shreds of fibrin passed through the alveolar pores. The mucosa of the bronchioles showed thinning and areas of desquamation. Peribronchial fibrosis was common. The bronchial cartilages in the left lung were extensively destroyed by tumor cells. Diagnosis: Squamous cell carcinoma.

CASE 4 (No. 9816). White male, aged 36, anthracite coal miner 20 years, was admitted on December 19, 1936, complaining of dyspnea, hemoptysis, cough, expectoration and fullness in the epigastrium. Dyspnea set in a year ago. During the last 6 months the patient had fullness in the epigastrium with some cough, expectoration and occasional hemoptysis. The family history was negative and there was no past history of influenza.

Physical Examination. Chest was rounded. Expansion was fairly good on both sides with normal vocal fremitus. Over the right upper lobe was dullness but the breath sounds were easily heard. Over the remainder of the right lung and the entire left lung the percussion note was resonant and the breath sounds were loud and well heard. No râles. Heart was displaced to the right. Liver was enlarged and nodular. The sputum was negative for tubercle bacilli.

Roentgen Ray Examination (Fig. 9) showed haziness in the right upper lobe region. Throughout the remainder of the right lung and the entire left lung were increased tissue markings. The trachea and the heart were displaced towards the right.

Temperature was normal. Pulse rate was from 80 to 90, and respiratory rate from 25 to 35 per minute.

The patient died on December 27, 1936.

Necropsy. Both lungs showed scattered anthracosilicotic nodules measuring from 1 mm. to 4 mm. The right upper lobe was atelectatic due to a hard tumor constricting the lumen of its bronchus. Within the center of the atelectatic lobe was a large cavity containing blood-tinged necrotic material. The lower lobe of each lung showed scattered tumor nodules. There was considerable peribronchial and perivascular fibrosis. Some of the blood-vessels were thrombosed.

Microscopic Examination. The tumor consisted of small round cells with very scanty cytoplasm densely packed and very little intercellular stroma. Some cells formed glandlike structures. The bronchial cartilages were extensively destroyed by tumor cells (Fig. 10). There was peribronchial and perivascular fibrosis. The lymph vessels were filled with tumor cells. Some blood-vessels showed thrombi containing tumor cells. Adjacent to the thrombotic vessels were areas of infarction, some of which had undergone necrosis. The anthracosilicotic nodules were broken up by tumor cells. Diagnosis: Carcinoma, undifferentiated type.

Discussion. The outstanding clinical features in these cases were dyspnea, hemoptysis, cough, expectoration and pain in the chest. These symptoms, except for hemoptysis, are the usual manifestations

in long standing anthracosilicosis. Though hemoptysis may occur in association with pulmonary tuberculosis, in pure anthracosilicosis it is rare. Due to the absence of any unusual clinical findings but only those complaints commonly encountered in anthracosilicosis complicated by pulmonary tuberculosis, these cases were regarded as anthracosilicosis with pulmonary tuberculosis, until suspicion was aroused by the repeatedly negative sputum examinations. The sputum may be repeatedly negative for tubercle bacilli in anthracosilicosis with pulmonary tuberculosis, but in cases in which hemoptysis occurs tubercle bacilli are usually found. The negative sputum for tubercle bacilli in anthracosilicosis with hemoptysis a frequent symptom, should arouse suspicion for malignant disease of the bronchus.

Dyspnea was the earliest and most prominent symptom in every case partly due to preëxistent anthracosilicosis with concomitant emphysema. In all the cases there was widespread destruction of the bronchial cartilages. The tumor cells in the peribronchial lymphatics penetrated through the vessel walls and invaded the bronchial cartilages. In some areas the bronchioles appeared collapsed due to destruction of the cartilages and one may surmise that in such a case the ingress and egress of air must have been seriously interfered with.

Although there was extensive cavitation with retention of necrotic matter in Cases 1, 3 and 4, the common symptoms of pulmonary abscess, such as fever and chill, were lacking. This could be due to slow absorption of the toxic material on account of an impairment of the lymphatic circulation resulting from anthracosilicosis. Furthermore, a Roentgen ray examination of the pulmonary artery in Case 4 (Fig. 11) shows a distinct decrease in the number and caliber of its ramifications in the atelectatic right upper lobe, within the center of which was a large cavity containing necrotic matter. One may assume that the circulation in this lobe was impaired, and was capable of absorbing only a small amount of the toxic substance.

Farrell² stated that the most constant Roentgen ray finding in bronchial carcinoma is evidence of collapse of the lung in part or as a whole and the least characteristic of the frequently encountered changes secondary to bronchial new growths is an increase in the linear markings. These markings, he observed, were often looked upon as due to some non-specific inflammation; though, when it occurred in the upper portions of the lung fields, it was often diagnosed as tuberculosis and in the lower as bronchiectasis. In Cases 1, 3 and 4, the Roentgen ray appearance was characteristic of pulmonary atelectasis due to a bronchial occlusion. Case 2 lacked the usual Roentgen ray signs of bronchial carcinoma. The dense opacity in the right lower lobe area was due to pleural effusion. The exaggerated linear shadows in the lungs resulted from peribronchial

and perivascular fibrosis, and invasion of the lymph channels by tumor cells. The scattered small nodular shadows throughout the lungs, particularly about the hilum regions were due to the anthracosilicotic and tumor nodules. On account of tumor cells surrounding them, the anthracosilicotic nodules lacked the usually sharp outlines.

The principal histopathologic feature in these cases was the extensiveness of destruction of the anthracosilicotic nodules by the tumor cells. Some of the anthracotic nodules consisted of collapsed alveoli, the walls of which contained much pigment. They were easily pushed apart by tumor cells filling the alveolar spaces. In the center of some of the anthracosilicotic nodules were small lymph vessels filled with tumor cells. Some cells broke through the walls of the lymph vessels and invaded the anthracosilicotic nodules. The acellular central portions of the silicotic nodules were free of tumor cells, but their cellular peripheral zones were thickly crowded with them. In spite of fibrosis the perivascular and peribronchial lymphatics were capable of tremendous dilatation and engorgement by tumor cells.

In Cases 2 and 3, small tumors disrupted the bronchial mucosa and discharged tumor cells into the bronchial lumen. The mucous material in the bronchi became loaded with tumor cells. Entrance of mucus containing tumor cells into the non-involved parts of the lung appeared to be an important metastatic factor. Tumor cells passing through the alveolar pores were observed. Unquestionably, the lymphatics played an important rôle in intrapulmonary metastasis in these cases. In Case 2, a sagittal section of a thin thread-like adhesion between the middle and lower lobes showed that the tumor cells from the surface of the visceral pleura covering the lower lobe had entered the adhesion. Many blood-vessels in all the cases showed thrombi containing tumor cells.

The cavities in the atelectatic lobes must have resulted from evacuation of the abscesses resulting from an interference with the normal bronchial drainage. Small areas of necrosis were observed in all the cases and they seemed to have resulted from pulmonary infarction caused by tumor cells occluding the blood-vessels. The areas of infarction were most numerous in the right lower lobe of Case 2 and the left lower lobe of Case 3. Many tumor nodules showed central necrosis.

According to Fischer-Wasels³ cancer develops when the germ plasm having cancer tendency is irritated by such factors as tobacco smoke, tar, dust, acute or chronic disease. Unquestionably, the bronchial mucosa and the pulmonary tissues in these cases were irritated by the particles of coal and silica over a long period of time. Such chronic irritation might well have had some influence on the development of carcinoma in these cases.

Summary and Conclusion. 1. Clinical and pathologic observations on 4 cases of primary carcinoma of the bronchus associated with anthracosilicosis are briefly described.

2. Dyspnea, hemoptysis, cough, expectoration and pain in the chest were the outstanding symptoms. Sputum negative for tubercle bacilli (with hemoptysis a frequent symptom) excited a suspicion of primary malignant growth of the bronchus.

3. Roentgen ray diagnosis of diffuse bronchogenic carcinomatosis is difficult when anthracosilicosis coëxists.

4. Extensive destruction of the bronchial cartilages, resulting in collapse of the involved bronchi, might have been responsible for severity of dyspnea.

5. Capability of the peribronchial and perivascular lymphatics to dilate in spite of fibrosis surrounding them was noted.

6. Spread of tumor cells through the alveolar pores and interlobar adhesions was observed.

7. Absence of toxic symptoms of pulmonary suppuration was attributed to impaired lymphatic absorption and lessened blood flow through the atelectatic lungs.

8. A suggestion is made that in these cases anthracosilicosis might have had an indirect influence on development of carcinoma of the bronchus.

The writer desires to tender his thanks to Dr. Frank A. Craig for his permission to use the Sanatorium material and to Dr. Joseph Walsh for his valuable criticisms and permission to use the necropsy specimens.

REFERENCES.

- (1.) Allen, M. L.: *J. Indust. Hyg.*, 16, 346, 1934. (2.) Farrell, J. T., Jr.: *Radiology*, 26, 267, 1936. (3.) Fischer-Wasels, B.: *Klin. Wchnschr.*, 11, 1937, 1932; *Deutsch. med. Wchnschr.*, 59, 1489, 1933. (4.) Pancoast, H., and Pendergrass, E. P.: *J. Am. Med. Assn.*, 101, 587, 1933. (5.) Sokoloff, M. J.: *Am. Rev. Tuberc.*, 34, 700, 1926.

MASTITIS IN THE MALE.

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Of all swellings of the male breast, that produced by an acute or chronic mastitis is the most frequent. Tumors of the male breast do not differ essentially from those seen of the female, except as modified by the anatomy of a non-functioning rudimentary organ.

Of all tumors of the mammary gland only approximately 1% occurs in males. Since chronic irritation in the mammary glands of females frequently is followed by malignant changes, it might be expected that the mammary glands of males also would show malignant changes frequently. Such, however, is not the case, as is apparent by an examination of the rather extensive literature upon the subject. The earlier literature seems to indicate that a large per-

centage of swellings of the mammary gland in males is malignant, benign conditions being rarely seen. Reports of the past few years give an entirely opposite view. The occurrence of malignant tumors in the male is relatively uncommon.

This report is based upon a study of 25,689 patients admitted to a single institution during a recent 5-year period. In only 1 instance was a malignancy of the breast found. During the same period 16 males were found with benign swellings of the breast.

The differentiation between decidedly malignant tumors of the breast and a chronic mastitis is not difficult; but benign and very early malignant lesions are often very difficult to distinguish and especially where chronic inflammation has existed for some time. Not only may chronic productive mastitis result in overgrowth of epithelium and connective tissue, which may gradually pass into malignant manifestations, but senile involution may also be accompanied by irregular production of epithelium and stroma (Ewing⁵).

Cheate^{2b} emphasizes the occurrence of desquamation of the proliferated epithelial cells within the ducts and acini, and often papillary overgrowth. The atypical proliferation that may follow, with some cells exhibiting signs of malignancy, he considers a pre-cancerous state.

The history of mammary malignancies is usually that a chronic inflammatory process preceded the malignancy, and that the development of the tumor was slow and insidious. Since malignant tumors appear frequently to arise on chronic mastitis, removal of such a minor condition seems definitely justified.

The normal anatomy of the male breast has received far less careful study than has that of the female breast. Most textbooks devote little space to a description of a normal male mammary gland, usually being satisfied with the statement that it contains only rudiments of gland structures. Andrews and Kampmeier¹ have shown, however, by careful dissection that in every male breast there is a complicated system of ducts and alveoli and "that in adult males the breast tissue persists in essentially the same state as the pre-adolescent female." The ducts and alveoli are lined by a single layer of columnar epithelium and the ducts are invariably patent. The glandular structure is sharply limited from the connective tissue by a limiting membrane. The fibrous areas about the ducts often resembles proliferating fibrous tissue.

There are two important predisposing etiologic factors in mastitis of males. Trauma, a single injury, or continued irritation such as the rubbing of a mail pouch across the nipple was apparently an etiologic factor in 2 of the cases presented here. The second factor is a dirty skin, one that harbors pyogenic bacteria in large numbers, which when rubbed into a traumatized glandular structure find a suitable soil for growth. There is no evidence that infection is hematogenous although such a source is not impossible. The

presence of infection elsewhere adds to the chances of infection of the skin in the region of the breast and subsequent involvement of the ducts. Two patients in this series gave a history of a single severe trauma. Two others, letter carriers, attributed the condition to irritation by the strap of the mail sack. The remainder gave no history of injury. All were working men of apparently uncleanly habits. Six were machinists exposed to much heat and dirt. It is not surprising that acute and chronic infection develops in such a complicated glandular structure with ducts open to receive infection and with stagnation of the small amount of secretion present to act as a culture media.

Acute mastitis may occur in the male and occasionally progresses to abscess formation. Of 3 cases of acute mastitis presented here, in 2 a definite abscess was present. The usual course, however, is that of a subacute infection which tends to progress into a chronic state.

Chronic mastitis is the most frequent cause of enlargement of the male breast. In the female at least three types of "chronic mastitis," based upon anatomical and pathologic findings, are seen (chronic glandular mastitis, chronic interstitial mastitis, and senile involution). In the male breast differentiation cannot well be made; the clinical and pathologic findings resemble more closely the chronic interstitial type of mastitis of females.

In this group of cases there was a visible change, most marked for from 3 to 5 cm. about the nipple. The tumor was tender and freely movable. Except in the acute cases there was no redness. I have never seen any secretion from a male breast, nor could pus be expelled. The axillary glands in chronic mastitis were seldom tender and only slightly palpable.

The microscopic findings of chronic mastitis are slight round-cell infiltration about the ducts, increased vascularity, an edema of the fibrous stroma about the alveoli and ducts, with resulting increase in the fibrous elements. Especially in circumscribed areas, the process may resemble adenofibroma.

One case of this series should perhaps be diagnosed gynecomastia. The smooth rounded breast, approximately 5 inches in diameter, resembled that of a female. However, the evidence for mastitis indicated that chronic infection might have brought about an overproduction of fibrous tissue, so that the so-called gynecomastia was a manifestation of long-continued chronic irritation. In this case, no changes were present in the testicles nor were other sexual characteristics altered, and none should be expected if it is the result of chronic infection.

Treatment of acute mastitis in males does not differ from that encountered in the non-lactating breast of females. Excision of the mammary tissue is the only safe procedure. Carcinoma of the male breast does occur and particularly as the result of long-con-

tinued irritation. The manifestations of the clinical course are so similar and the determination of the actual condition so difficult, that in a large percentage of instances an absolute diagnosis without removal of the breast is impossible. If one is in doubt, and one can hardly be otherwise in the presence of a firm tumor involving a glandular structure, operation is the only safe choice. The chief hope for the reduction of carcinoma in the male breast lies in excision of all breasts showing chronic mastitis. The loss of a non-functioning rudimentary glandular structure is of little importance, and it is far better to sacrifice 10 male mammary glands needlessly, than to allow 1 to progress to malignancy with its resulting serious sequelæ.

Case Abstracts. CASE 1.—An engineer, aged 32, stated that he had noticed a swelling of the left breast for about 5 years, which was becoming larger. The tumor was freely movable beneath the nipple and not adherent to the underlying muscle. There was no adenopathy. The temperature was not elevated. The removed tumor appeared to be due to mastitis. Microscopically, the bulk of the mass was composed of dense fibrous tissue in which were scattered well-defined glandular structures, whose epithelium was hyperplastic to the extent of presenting in some areas two or three layers of cells, as is frequently seen in fibroadenoma. Some periductal round-cell infiltration was present. Evidence of malignancy was lacking.

CASE 2.—A letter carrier, aged 63, stated that he noticed a swelling of the left breast for 1 month. He stated that the strap of his mail pouch continually rubbed the breast. This he believed was the cause of the swelling. Examination revealed a tumor of the breast 5 cm. in diameter, which was not adherent to the nipple nor to the underlying structures. The tumor was removed. Microscopically, it consisted of dense fibrous tissue through which were scattered small islands of glandular tissue. Some periductal infiltration was present. The ducts were lined by a single layer of epithelium. It was a subacute or chronic mastitis.

CASE 3.—A letter carrier, aged 42, stated that for about 1 month he had noticed a swelling of the right breast which was moderately tender. He was left-handed so that he carried his mail bag on his right shoulder and he thought the swelling was due to the rubbing of the strap. Examination showed a tender mass 3 cm. in diameter beneath the nipple. It was not adherent to the underlying structures. The breast was removed. Sections showed hyperplasia of glandular acini usually with two or three layers of epithelium. There was moderate round-cell infiltration in the periductal tissues. The findings were those of a subacute or chronic mastitis.

CASE 4.—A man, aged 64, retired, stated that he had noticed a tender swelling of the right breast for about 1 month. Examination revealed a tumor mass approximately 4 cm. in diameter. It was not adherent to the deeper structures. The breast was removed. Sections showed scattered areas of glandular tissue lined by a single layer of columnar epithelium embedded in a stroma of fibrous connective tissue. Moderate periductal round-cell infiltration was present. Impression subacute or chronic mastitis.

CASE 5.—A young man, aged 21, stated that he had noticed a swelling of the right breast for the past 2 months. There was some pain and moderate tenderness. Examination revealed a swelling of the breast about 4 cm. in diameter. The breast was removed. Microscopic sections showed a dense fibrous stroma in which were scattered acini with regular formed but

with thickened epithelium. Periductal infiltration of round cells gave evidence of a subacute or chronic mastitis.

CASE 6.—A young man, aged 27, stated that he had noticed a tender lump in the left breast for the past 6 months. There had been little pain but the breast was tender. Examination revealed a small mass beneath the left nipple not adherent to underlying structures. The breast was removed. Microscopically, sections revealed glandular epithelium lined with a single layer of columnar epithelium scattered throughout a dense fibrous stroma. There was moderate periductal round-cell infiltration. Subacute mastitis.

CASE 7.—A man, aged 29, stated that for the past 2 months he had noticed that the right breast was tender and somewhat painful at times. The condition had changed little since the onset. Examination revealed a hard swollen tender mammary gland on the right side. The mass was approximately 7 cm. in diameter. On incising into the gland a small amount of purulent material was expelled. Acute mastitis.

CASE 8.—A man, aged 22, stated that for several years he had noticed a lump in the left breast and that for the past 10 days the swelling had been very tender. Examination showed a breast about 4 inches in diameter resembling in size and shape a female breast. It was apparently tender. The infection subsided with wet dressings, and the patient refused to have the breast removed. Clinically, this case was one of gynecomastia with infection of the breast tissue.

CASE 9.—A man, aged 52, stated that for the past 5 months he had noticed a tumor of the left breast which had increased somewhat in size. There was some tingling pain but no tenderness. Examination showed a mass 7 cm. in diameter which was attached to the overlying skin and to the muscle sheath beneath. The axillary glands were enlarged. Radical removal of the breast and lymph nodes was done. Sections showed adenocarcinoma in both the breast and lymph glands.

CASE 10.—A man, aged 22, stated that 6 months before he had had an empyema drained on the left side. While this was still draining, the right breast became sore and tender. While the tenderness had become less, it continued to annoy him somewhat and slight tenderness persisted. Examination revealed a tender swelling of the right breast 4 cm. in diameter with slight redness of the skin.

CASE 11.—A man, aged 41, complained of a tender swelling of the left breast for the past 3 months. It has grown somewhat during that time. The breast was removed. Sections showed a chronic mastitis.

CASE 12.—A boy, aged 17, stated that the left breast had been large for at least 2 months. He had never noticed any soreness nor other symptoms, but a friend had told him at that time that the one breast looked like a girl's. The breast was removed. Section of the breast showed a fibroadenoma.

CASE 13.—A man, aged 45, stated that 7 weeks previously he had noticed a tender swelling of the left breast. He thought there was some increase in size during the past month. The breast was removed. Sections showed an epidermoid cyst, infected, lying in the mammary tissue.

CASE 14.—A young man, aged 21, stated that 5 months previous he had noticed a tender lump in the left breast which he thought had increased in size. There has been no pain but the breast has remained tender. The breast was excised. Microscopic sections showed a fibroadenoma with some periductal round-cell infiltration.

CASE 15.—A young man, aged 21, stated that 1 month before he had been struck on the left breast. Since then the breast had been tender and somewhat painful. It was removed. Sections showed scattered ducts

lined with simple and stratified columnar epithelium. There was some periductal round-cell infiltration.

CASE 16.—A man, aged 35, complained of a tender swelling of the left breast of 10 days' duration. The tender, swollen breast was excised. Sections showed an acute and subacute inflammation.

CASE 17.—A man, aged 63, under treatment for another condition, complained of a tender swelling of the right breast. Examination showed a firm rounded swelling 4 cm. in diameter beneath the right nipple. There was moderate tenderness. Excision was advised but refused by the patient.

Summary. Seventeen swellings of the male breast are reported, 1 of which was malignant.

The male breast is a well-developed glandular structure, and as such is subject to the same pathologic processes as occur in the non-lactating female breast.

Subacute or chronic mastitis is the pathologic condition most frequently encountered. It may change to fibroadenoma or occasionally to carcinoma.

Treatment of chronic mastitis in the male should include excision of the mammary tissue, as the loss of a rudimentary gland is of little importance and carcinoma may thus be prevented.

BIBLIOGRAPHY.

- (1.) Andrews, E., and Kampmeier, O. F.: *Surg., Gynec. and Obst.*, 44, 30, 1927. (2.) Cheate, G. L.: (a) *Brit. J. Surg.*, 10, 436, 1923; (b) *Brit. Med. J.*, 1, 653, 1924; (c) *Ibid.*, 1, 5, 1925; (d) *Arch. Surg.*, 13, 617, 1926; (e) *Ibid.*, 17, 535, 1928. (3.) de Cholnoky, T.: *Am. J. Surg.*, 30, 298, 1935. (4.) Erdman, J. F.: *Am. J. Med. Sci.*, 168, 799, 1924. (5.) Ewing, J.: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 3d ed., 1928. (6.) Judd, E. S., and Morse, H. D.: *Surg., Gynec. and Obst.*, 42, 15, 1926. (7.) McFarland, J.: *Ibid.*, 45, 729, 1927. (8.) Theille, L. A.: Reported by Ewing, J. (Ref. 5). (9.) Wainwright, J. M.: *Arch. Surg.*, 14, 836, 1927.

THE DIAGNOSTIC VALUE OF SUPRAVITAL STAINING IN INFECTIOUS MONONUCLEOSIS.

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GLANDULAR fever was long confused with a relatively large group of diseases producing generalized lymph node and splenic enlargement. It was not until 1920, that the clinical syndrome, the characteristic blood picture, and the benign course were correlated by Sprunt and Evans who coined the term infectious mononucleosis.¹⁶ The hematologic characteristics were thoroughly investigated by Downey,^{6,7a b} Baldrige, Rohner, and Hansmann,¹ Nyfeldt,¹¹ and Lehdorff and Schwarz.¹⁰

As medical consciousness of the disease waxed, the difficulty of definitely distinguishing it from several other disease entities be-

came evident. Note was variously made concerning its resemblance to leukemia, tuberculosis, Hodgkin's disease, agranulocytic angina, Vincent's angina, and postinfectious lymphocytosis. In 1932, however, Paul and Bunnell¹⁴ accidentally recognized the presence of heterophile agglutinins and hemolysins for sheep cells in patients suffering from the disease and subsequent clinical application has revealed considerable specificity of this reaction.^{15,16} Although the agglutinins occur under a variety of circumstances^{17,18} and on occasion may not be present in this disease,¹⁹ they have proved a definite aid in distinguishing infectious mononucleosis from the diseases for which it may be mistaken. In fact, the clinical manifestations of the disease are so variable that a recognition of its presence depends entirely upon both serologic and morphologic study of the blood.

Unfortunately, as the result of increasing emphasis upon the serologic aspect of diagnosis associated with the apparent difficulty of the unpracticed, and all too frequently, the practiced eye in definitely identifying the predominant cell in the peripheral blood;^{2,4,5,11,20} the marked variation in the clinical syndrome; and confusing references to non-monomuclear types and phases of mononucleosis, the heterophile antibody reaction is rapidly being accepted as the prime and occasionally sole factor in diagnosis.²¹ This has created a recognizable trend toward removing the establishment of the diagnosis from the province of the physician and placing it into the hands of the laboratory technician. Excessive reliance, however, upon any single laboratory procedure, regardless of how well understood and tested it may be, has always proved dangerous in any diagnostic field. An additional criterion, if simply applicable, and confirmed in reliability, must therefore, have practical value. With this in mind, note will be made of readily elicitable morphologic features which serve to establish with ease and rapidity the identity of infectious mononucleosis.

It has been claimed that certain criteria manifest themselves in the appearance of the specific cell of the disease, but in view of the varied nomenclature employed (atypical lymphocyte, immature lymphocytes, lymphoblast, monocyte, mononuclear cell, etc.), it is evident that widespread confusion exists concerning its identity. Despite the increasing interest in the disease, little attention has been directed toward the appearance of the living cells, a state in which they may be conclusively diagnostic. McLean,²² Nyfeldt,²³ and Wilson and Cunningham²⁴ have described the appearance of the cells of infectious mononucleosis when stained supravitaly by neutral red and Janus green. The method which has a very definite value in supplementing the ordinary clinical measures, will readily confirm the diagnosis of infectious mononucleosis.

Material and Methods. One or more blood specimens obtained from each of 21 individuals suffering from subsequently proved infectious mono-

nucleosis were studied by fixed smear and moist supravital stained preparations. Ordinary slide smears of peripheral blood were dried in air and stained with a combination of Wright and Giemsa stains. Blood obtained from the same puncture wound was in each case placed upon 3 clean glass slides—one bearing a dried film of neutral red and Janus green, another a film of neutral red alone, the third slide containing no dye at all. Each drop of blood was covered by a thin coverslip applied without pressure. The method has been described in detail elsewhere.⁸ Such preparations even without sealing or warmth remained adequate for study for as long as 2 to 4 hours. The warm box offered little advantage except for studies of cell motility and was therefore utilized only for such observations. At room temperature adequate staining of cytoplasmic structures occurred within 15 to 20 minutes and a temperature of 37° C. motility was evident in about 10 minutes.

Each of the cases had determinations of the heterophile antibody titer and all except one showed titers within the range established by Davidsohn,⁵ Paul and Bunnell,¹⁴ and van Ravenswaay¹⁸ as being that commonly found in the disease. The one exception presented clinical and hematologic criteria unmistakably characteristic of glandular fever, although at no time were there evidences of sheep cell agglutinins above a dilution of 1 to 30. Such exceptions have been noted previously.^{4b,c} The absence of heterophile agglutinins was consistently observed in many other cases with less characteristic lymphocytoses.

Observations. A. Refractile Granules. In the course of earlier observations there had been noted within circulating lymphocytes a peculiar refractile granule visible in unstained preparations and assuming a mahogany tint with neutral red.^{8a} Subsequent studies established the constancy of the occurrence of these granules in approximately $\frac{1}{3}$ of lymphocytes in wet preparations.^{8b} Confirmatory observations have since been published by Whitby and Hynes.¹⁹ In conjunction with the present series of cases of infectious mononucleosis, moist blood preparations have been obtained from 137 additional individuals and have been examined with particular reference to the presence of refractile bodies. In accordance with the preëxisting data they were present relatively constantly in more than 25% of the lymphocytes. This group included 52 normal persons and 85 patients with a variety of diseases. On rare occasions the granule-bearing cells have been fewer than 25% of the total number of lymphocytes, but in only 9 did they constitute less than 20%. No question of diagnosis arose in any of these exceptional cases since all had lymphocytes well within the normal range numerically and morphologically. In the great majority of the remainder the refractile bodies were present to the extent of 30 to 50%, the average for the entire 137 cases being 31.1%.

In a previous publication note had been made of a single exception to this rule wherein the percentage of granule-bearing lymphocytes was less than the established minimum.^{8b} This blood had been obtained from a case of infectious mononucleosis and with interest thus directed the 20 additional cases in the present series were examined with the intent of determining the frequency of the pecu-

liarity in this disease. In none were the lymphocytes containing granules in excess of 15% during the acute disease, nor was there any striking variation of this phenomenon in either the apparently normal or obviously abnormal cells, the former exhibiting as much of a diminution of granules as the latter.

In seeking for these cases of glandular fever opportunity to examine bloods from cases resembling it in one way or another was afforded in 33 instances. The cases included in this subgroup presented lymphocytoses between 50 and 88%. Several of the specimens were obtained from infants and young children. In

TABLE 1.—LYMPHOCYTES AND THEIR GRANULES IN VARIOUS DISEASES

Group	Subgroup	No. cases	Average % granules	% granules	Mean %	St. dev.	% granules	% granules
I	Lymphocytosis	5	18.7	10.0	4.7	22	0	0
Lymphomatoid diseases	Hodgkin's	2	17.2	10.7	4.7	22	0	0
II	Arteriosclerosis	2	23.0	17.0	6.7	32	0	0
Miscellaneous blood diseases	Pernicious anemia	1	42.5	24.0			0	0
	Hypochromic anemia	2	21.5	15.5	4.5	6	0	0
	Polycythemia vera	3	16.3	14.0	4	15	1	0
	Polycythemia vera	1	25.0	22.0			0	0
III	Myeloblastic	5	7.6	41.4	61	27	0	0
Leukemias	Lymphatic	7	11.0	35.0	47	18	1	0
	Plasma cell	1	88.0	15.0			1	0
IV	Normal	52		24.0	57	14	1	1
V	Miliary	1	10.5	47.0			0	0
Tuberculous	Peritonitis	1	28.0	35.0			0	0
	Pulmonary	14	14.7	24.0	52	22	0	0
VI	Acute	17	23.7	38.0	69	16	1	0
Infectious diseases	Subacute	7	37.0	33.5	47	29	0	0
VII	Miscellaneous	11	23.0	37.0	54	19	1	0
VIII	Infectious mononucleosis	21	61.2	11.2	15	5	21	21

many, reasonable clinical doubt as to differentiation from infectious mononucleosis had existed. In only one of the group, however, did the granule-bearing lymphocytes approach the critical minimal level and this was a case of leukemic plasma-cell leukemia. The appearance of the component elements of this blood smear, however, was such that confusion with infectious mononucleosis was impossible. Graphic representation of this group is demonstrated by Group IX in Figure 1.

Analyses of the percentages of granule-bearing lymphocytes present in the various groups accumulated are shown in Table 1 and Figure 1. The wide range of the percentages in the normal group and those diseases exclusive of infectious mononucleosis is in sharp

distinction to the group of infectious mononucleosis. Reference to the minimal levels in the control Groups I to VII demonstrates the sparsity of bloods containing fewer than 20% lymphocytes with refractile granules. In contradistinction to these groups, Group VIII, consisting of the 21 cases of glandular fever, shows a maximal

PERCENTAGE OF LYMPHOCYTES CONTAINING REFRACTILE GRANULES.

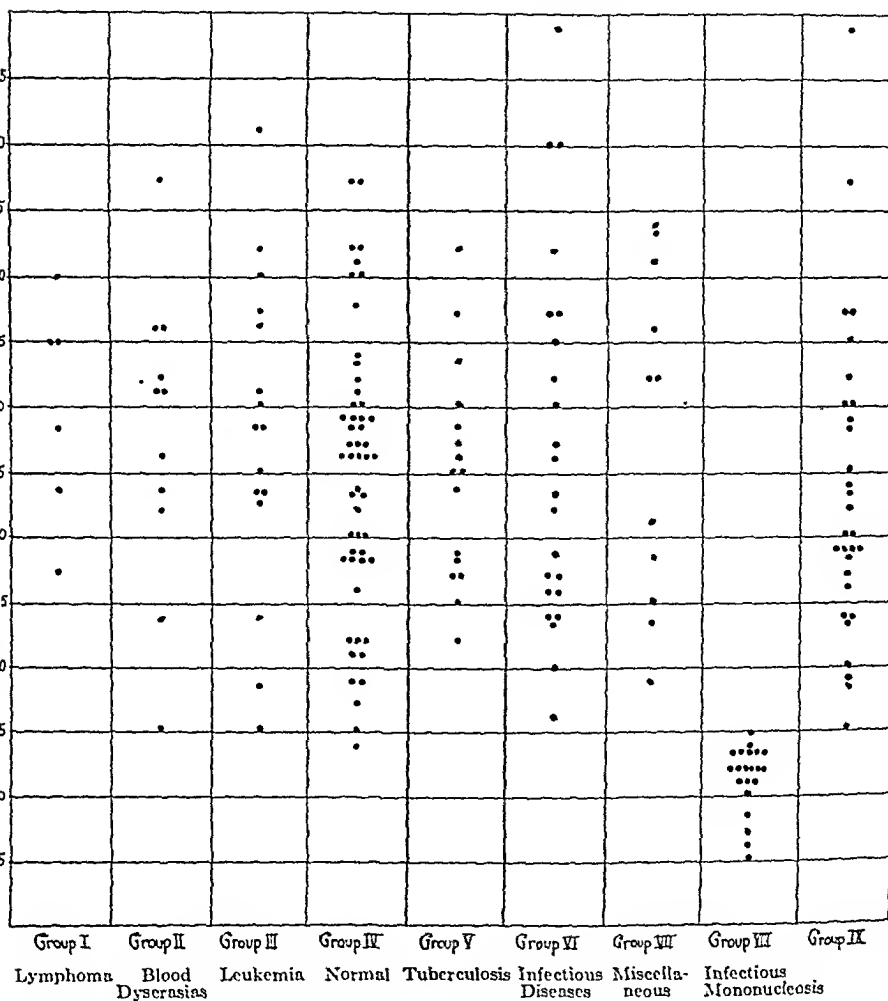


FIG. 1.—The diagnostic value of supravital staining in infectious mononucleosis.

level of 15% with an average content of 11.6%. Equally striking was the persistence of this dearth of granule lymphocytes for several weeks to months after the disease had subsided clinically. Marked variation in the length of time required for subsidence of minor clinical evidences of the disease has been noted in the literature.^{1,11,14,16}

Ordinary moist unstained preparations were adequate for identification of the refractile granule-bearing lymphocytes and approximately 30 minutes were necessary to perform a differential count of 200 cells. Facility in recognizing the various cells was naturally enhanced, however, in those preparations stained with neutral red and Janus green and certain other characteristics were demonstrated which warrant detailed description.

B. Supravital Studies. The cells in infectious mononucleosis varied considerably in size and shape and most of them showed motility at one time or another when kept at 37° C. and not infrequently at room temperature as well. The motility was always lymphocytic in character inasmuch as the nucleus remained at the fore end of the moving cell and the cytoplasm streamed behind in a tail-like fashion. At no time was the surface film movement distinctive of monocytes observed in these cells.¹² The presence of Janus green in the stain film inhibited motility markedly.

Nuclei were relatively large, eccentric, and filled from one-half to three-fourths of each cell. The configuration was generally reniform although in the motile cells and the small immobile lymphocytes bizarre contours predominated. Chromatin, which was only visible with lessened illumination, exhibited a coarse smudgy appearance and a fluted or grooved arrangement of the chromatin strands was frequently perceived. No nucleoli or mitoses were encountered but occasionally a nucleus in the process of amitotic division or two discrete nuclei in a single cell were seen. Occasional lymphocytes contained nuclei indistinguishable from those in plasma cells, with coarse clumped chromatin smudges frequently aggregated at the nuclear margin and a comparatively thick, slightly refractile nuclear membrane. These cells were similar in all other respects to the lymphocytes encountered in this disease.

The cytoplasm generally presented the characteristic hazy, faintly opaque appearance of normal lymphocytes distinctive from the finely granular, ground glass cytoplasm of the monocyte. The mitochondria in the small lymphocytes and many of the intermediate lymphocytes were moderately coarse, short, rod-shaped, and globular particles staining bright greenish blue with Janus green. These were exactly similar to those observed in normal lymphocytes but in the remainder of the intermediate and all of the large lymphocytes the mitochondria were predominantly rod-shaped, slightly less numerous, and considerably larger than in the normal cell. Furthermore, although a few of the smaller mitochondria remained in the vicinity of the nuclear border and frequently appeared to be superimposed upon the nucleus, the majority were dispersed throughout the cytoplasm in the portion contiguous with but peripheral to the bay of the nucleus. In the immobile cells they had the appearance of particles of bright bluish-green opaque substance suspended in a faintly yellowish, translucent gelatin. Such a cell

(Fig. 2) was demonstrated by Wilson and Cunningham²⁰ in a case of hemolytic streptococcus sore throat which from the scant data appended might equally well have been infectious mononucleosis.

Neutral red bodies were generally increased in number but retained the bright red refractile appearance normally noted in lymphocytes. These were generally distributed but exhibited a very pronounced tendency to clump on one side of the indented nucleus within its bay. They did not possess the regular arrangement of the true rosette appearing in the rabbit monocyte and less frequently in the human monocyte. This aggregation was therefore considered to be a pseudorosette. Such cells have been noted very occasionally in normal blood but never so frequently as they appear in infectious mononucleosis. Surrounding the neutral red aggregations there was usually an irregular halo of sparsely clustered mitochondria which rarely intruded upon the space occupied by the pseudorosette. In the motile cells the neutral red bodies retained their proximate relationship to one another behind the nucleus although the bay was usually obscured. Frequently the cytoplasm contained one to ten unstained vacuoles.

Distinction from the monocyte was therefore relatively simple, nor was there sufficient similarity to the immature lymphocytes to preclude differentiation. Lymphoblasts were similar in size but their nuclei were less frequently indented and usually filled more of the cell. The chromatin was less coarse, more regularly arranged, and nucleoli were usually evident. Neutral red bodies were not present and mitochondria were finer and clustered about the nuclear border. Occasionally such a cell was observed in infectious mononucleosis. Lymphocytes present in lymphocytic states such as pertussis and postinfectious lymphocytosis constantly adhered to the normal pattern. Details relative to the characteristic morphology of the cells cited above are enumerated in an earlier publication.^{8a}

C. *Dried Smears.* Cursory studies of fixed blood smears in this series revealed a predominance of those cells classed as Type I by Downey.^{6, 7a, b} These were not, however, deemed sufficiently characteristic to warrant differentiation from such cells as were seen in the postinfectious lymphocytoses and other lymphocytic states wherein large and intermediate lymphocytes made their appearance in large numbers. Furthermore, similar cells were abundant in the blood of normal infants and young children. Major distinction became sharply evident in the majority of cases only when the cells were viewed in the living state, stained supravitaly. Confusion of the Type I lymphocytes in the fixed smears with the lymphoblasts present in lymphatic leukemia was, however, minimized. The differential features outlined by Downey generally sufficed to establish distinction.

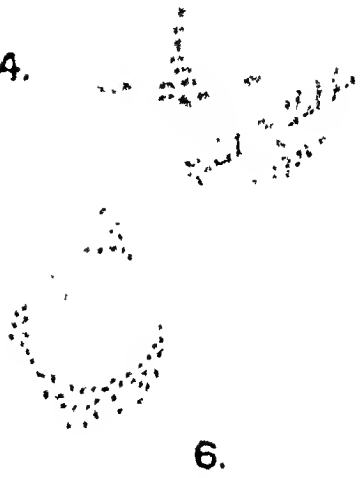
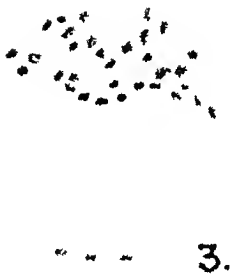
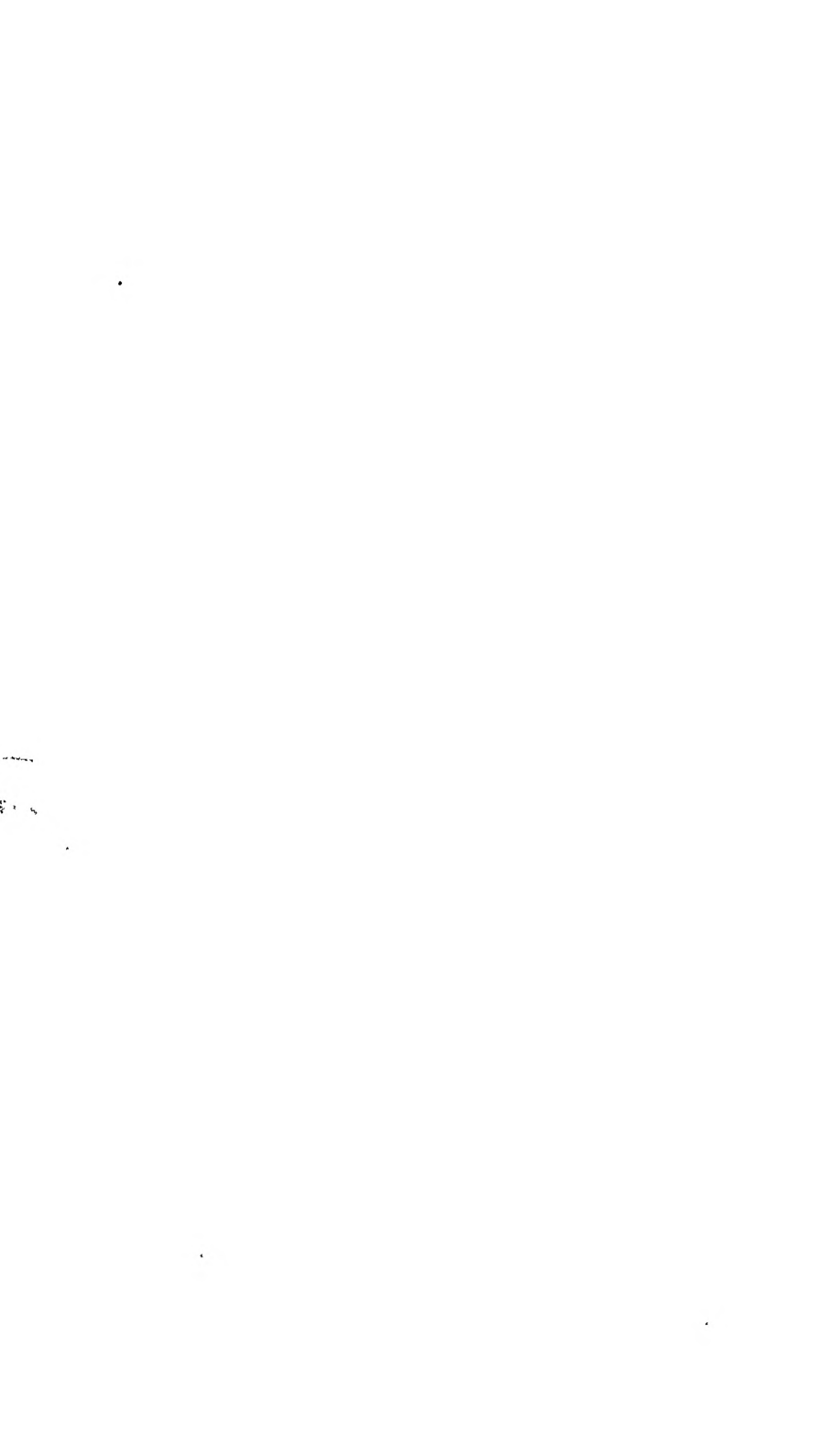


FIG. 2. -1, Normal monocyte. Note diffusely scattered mitochondria and neutral red bodies varying widely in size. 2, Small lymphocyte from a case of infectious mononucleosis. The mitochondria are coarse and the chromatin coarsened in appearance. 3, Intermediate lymphocyte in infectious mononucleosis. 4, Large lymphocyte in infectious mononucleosis. Neutral red bodies tend to conglomerate within the nuclear concavity to form a pseudorosette. 5, Normal lymphocyte. Chromatin is snudgy and finer mitochondria exhibit characteristic clumping. A single refractile body is present but there are no neutral red granules. 6, Lymphoblast. Mitochondria are grouped loosely about the nuclear border. Chromatin is relatively fine and a single nucleolus is present.

NOTE. A small clump of red blood cells is shown for size contrast. The red of the neutral red bodies and the blue of the mitochondria in the original colored illustration are naturally less distinct in monotone.



Discussion. Despite the contrary claims of Downey and his associates,^{1, 2, 3} it is evident that very definite difficulty may exist in differentiating the blood picture of infectious mononucleosis from that of other diseases producing a lymphocytic response.^{4, 5, 6, 7} Certainly, in view of the reasonable doubt expressed by individuals who have repeated contact with the disease, it is not too much to expect that those who encounter it less frequently will have considerably greater difficulty. Under such circumstances it is not surprising that so much stress is being applied to the presence of heterophile antibodies as a diagnostic measure. The test is unquestionably a valuable one, but it is occasionally geographically impractical and may be time consuming and relatively expensive. Furthermore, it is felt that application of the observations noted above will obviate to a certain degree the necessity of performing the test.

The characteristic lymphocyte of infectious mononucleosis is sufficiently distinctive in the living state to allow sharp differentiation from the cells present in lymphatic leukemia, infectious lymphocytosis (pertussis, etc.), and such monocytic reaction as occur in active tuberculosis. This is much less the case in the dried blood film. Its motility, protoplasmic content, and nuclear structure qualitatively proclaim the cell a lymphocyte, and the structural arrangement of these elements definitely establish it as a relatively mature but atypical cell. With regard to the postinfectious lymphocytoses and other clinical states with which the disease might conceivably be confused, the unique, constant, absolute decrease of lymphocytes bearing the specific refractile granules is a striking differentiating point. The term "absolute" is used advisedly for although both atypical and perfectly normal lymphocytes are present, the diminution of the refractile bodies is evident in both. It follows, therefore, that although otherwise normal such cells are lacking in structures present in all other conditions investigated. Table 1 and Figure 1 demonstrate the fact that specimens obtained from individuals with glandular fever never show extension of granule-bearing lymphocytes above the determined minimal normal level of 15%. This condition is sufficiently limited to infectious mononucleosis to warrant its utilization as a contributory diagnostic measure.

In view of the marked variance of prognostic significance attached to infectious mononucleosis and the many diseases which may at one time or another resemble each other both clinically and hematologically, the advisability of utilizing as many clinical diagnostic measures as may be available is evident. Although the determination of the presence of heterophile antibodies generally offers adequate confirmation, it is neither an absolute nor always a convenient diagnostic procedure. Other means of confirming clinical suspicion of glandular fever under conditions of minimal convenience are therefore not amiss. Conclusive diagnosis may be accomplished

by recognition of the characteristic supravitality stained blood cells and by determining the specific decrease of refractile granule-bearing lymphocytes regularly occurring in this disease.

Summary. 1. There is fairly generally admitted difficulty in definitely identifying the specific cell of infectious mononucleosis.

2. Despite the evident value of the determination of the presence of heterophile agglutinins, recognition of characteristic morphologic features of the typical cell of the disease would obviate its use to a great extent. Such features are evident in supravitality stained preparations.

3. By this means the cell is definitely shown to be an atypical but relatively mature lymphocyte readily distinguished from other mononuclear cells by several characteristics.

4. Refractile granules present in one-third of lymphocytes in other diseases and in the normal state are never present in higher than 15% of the lymphocytes in infectious mononucleosis.

REFERENCES

- (1.) Baldrige, C. W., Rohner, F. J., and Hansmann, G. H.: *Arch. Int. Med.*, 38, 413, 1926.
- (2.) Bloedorn, W. A., and Houghton, J. E.: *Ibid.*, 27, 315, 1921.
- (3.) Cady, L. D.: *Am. J. Med. Sci.*, 175, 527, 1928.
- (4.) Davidsohn, I. I.: (a) *Am. J. Dis. Child.*, 49, 1222, 1935; (b) Discussion following Ref. 7; (c) *J. Am. Med. Assn.*, 108, 289, 1937.
- (5.) Davidsohn, I. I., and Walker, P. H.: *Am. J. Clin. Path.*, 5, 455, 1935.
- (6.) Downey, H., and MacKinlay, C. A.: *Arch. Int. Med.*, 32, 82, 1923.
- (7.) Downey, H., and Stasney, J.: (a) *J. Am. Med. Assn.*, 105, 761, 1935; (b) *Fol. hæmatol.*, 54, 417, 1936.
- (8.) Gall, E. A.: (a) *J. Lab. and Clin. Med.*, 20, 1276, 1935; (b) *Am. J. Med. Sci.*, 191, 380, 1936.
- (9.) Kracke, R. R., and Garver, H.: *J. Am. Med. Assn.*, 104, 697, 1935.
- (10.) Lehdorff, H., and Schwarz, E.: *Ergebn. d. Inn. Med. u. Kinderh.*, 43, 1, 1932.
- (11.) Longcope, W. T.: *Am. J. Med. Sci.*, 164, 781, 1922.
- (12.) McLean, J. A.: *Med. J. Australia*, 2, 734, 1929.
- (13.) Nyfeldt, A.: *Fol. hæmatol.*, 47, 1, 1932.
- (14.) Paul, J. R., and Bunnell, W. W.: *Am. J. Med. Sci.*, 183, 90, 1932.
- (15.) Schenck, N. P., and Pepper, O. H. P.: *Ibid.*, 171, 321, 1926.
- (16.) Sprunt, T. P., and Evans, F. A.: *Johns Hopkins Hosp. Rep.*, 31, 410, 1920.
- (17.) Stuart, C. A., Burgess, A. M., Lawson, H. A., and Wellman, H. E.: *Arch. Int. Med.*, 54, 199, 1934.
- (18.) Van Ravenswaay, A. C.: *New England J. Med.*, 211, 1001, 1934.
- (19.) Whitby, L. E. H., and Hynes, M.: *J. Path. and Bact.*, 43, 91, 1936.
- (20.) Wilson, C. P., and Cunningham, R. S.: *Fol. hæmatol.*, 38, 14, 1929.

THE EFFECT OF THE INTRAVENOUS INJECTION OF HYPERTONIC DEXTROSE SOLUTION UPON THE CEREBROSPINAL FLUID PRESSURE IN CASES OF BRAIN TUMOR.

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THE intravenous injection of hypertonic dextrose solution as a means of dehydration in cases of increased intracranial pressure is quite general. The object of the study to be reported here was to determine the actual effect of such injections upon the cerebro-

spinal fluid pressures and hence upon the intracranial pressure in cases of brain tumor.

The original view of Faivre⁷ that the cerebrospinal fluid is unlike any of the other body fluids with the exception of the aqueous humor of the eye, is accepted by many physiologists. The manner in which the fluid is formed is a matter of dispute. Earlier workers, among them Magendie,¹¹ believed that it was formed by the leptomeninges. Faivre suggested that the cells of the choroid plexuses of the ventricles were concerned with its formation. Weed¹² and others suggested that perivascular tissue within the nervous system may contribute to the formation of the fluid. There is evidence also that ventricular ependymal cells in regions other than those of the choroid plexuses may secrete cerebrospinal fluid. This question has not been settled.

Likewise there has been no general agreement as to the route by which this fluid reaches the general circulation from the subarachnoid spaces. Key and Retzius,¹³ and Weed,¹² found that the major drainage occurs along the Pacchionian bodies, and that a slower drainage into the lymphatic system takes place along certain emergent nerves. The greater part of the cerebrospinal fluid escapes directly into the venous sinuses of the dura. Forbes, Fremont-Smith, and Wolf¹⁴ have shown that the direction of flow of the cerebrospinal fluid through the choroid plexuses may be reversed by increasing the osmotic pressure of the blood. They believe that the choroid plexuses may be regarded as semipermeable membranes and that the cerebrospinal fluid is a true dialysate. The plexuses would thus form a part of the mechanism for regulating intraventricular and intracranial pressure. Gamble⁶ has shown, and is so quoted by Fay,² that the fluid interchange between the vascular and interstitial compartments is facilitated by the fact that both are dependent upon a fixed base sodium for retention; whereas intracellular fluid is maintained by the fixed base potassium, and exchanges are not reciprocal. Therefore when fluid intake is restricted and elimination is forced, it is necessary that the interstitial reservoirs be drawn upon in order that the fluid volume may maintain its integrity. This is the principle upon which reduction of intracranial pressure by means of dehydration is based.

Reduction of brain volume and cerebrospinal fluid pressure by means of the intravenous injection of hypertonic solutions of various salts and of glucose was accomplished by Weed and McKibben¹⁵ in 1919. They found that the bulk of the brain could be controlled by a change in the concentration of certain elements in the blood stream which resulted in absorption of water from the tissues. In their work with cats they showed that the intravenous injection of hypertonic solutions caused an initial rise in the cerebrospinal fluid pressure which was followed immediately by a marked fall in pressure. Cushing and Foley¹ achieved like results. Foley and Putnam⁴ obtained similar effects by intrainestinal administration of hyper-

tonic solutions. In 1932, Milles and Hurwitz¹⁸ reported from animal experimentation that the reduction of cerebrospinal fluid pressures from single doses of dextrose was transient, and that a secondary rise occurred which reached a point much higher than the original level.

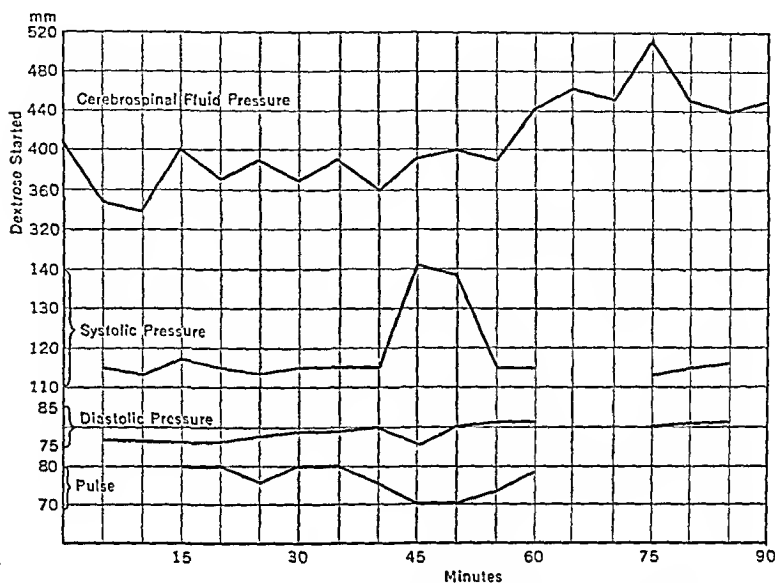


CHART I.—No. 308536. Brain tumor, right posterior frontal region.

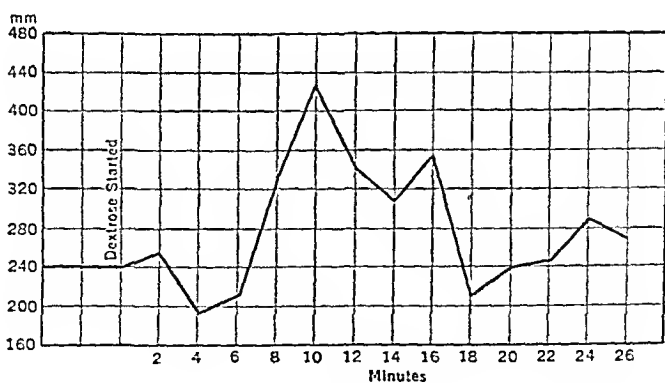


CHART II.—No. 306897. Spindle-cell sarcoma, right temporal region.

Kubie¹³ believed that there was a correlation between intracranial blood volume and intracranial pressure but not between the pressures themselves. Wolff and Forbes²¹ have shown that the administration of hypertonic solutions intravenously is followed by diminution of the caliber of the arterioles and venules of the pia, and that conversely, hypotonic solutions cause dilatation of the

vessels. Kubie and Hetler¹² demonstrated, by means of color photography, that following the intravenous injection of hypertonic solutions there is a narrowing of the vessels of the pia coincident with dilatation of the vessels of the cortex itself. It is probable that the total volume of the intracranial blood is increased as the volume of the intracranial fluid is diminished by the action of the hypertonic solution.

Varying results have been reported from the clinical use of hypertonic glucose solutions administered intravenously. Grant⁷ stated that the intravenous injection of 50% glucose produced a lowering of the cerebrospinal fluid pressure which was stationary providing the patient coöperated well. Masserman¹⁵ studied the effect of the administration of isotonic solutions in effective concentrations in 85 normal patients. He found that there was an initial increase in the cerebrospinal fluid pressure which was followed first by a fall in pressure and then by a secondary rise to levels which were from 8 to 148 mm. of water above the normal pressure. Jackson *et al.*,⁹ showed that in cases of injury to the brain, intracranial pressure not only may be appreciably lowered by the intravenous injection of hypertonic dextrose solutions, but may also be increased. He found an immediate increase in pressure in half of his cases and a slight temporary reduction of the pressure in the other half of his cases. In all cases there was a secondary rise in pressure after from 15 to 30 minutes. This secondary increase in pressure he considered to be due to pressure on the return venous flow in the sinuses of the brain.

Material. The material used for this study was composed of 6 cases of brain tumor in which the diagnosis was confirmed by subsequent surgery and pathologic report of the specimen, 2 cases of gumma of the brain, and 1 old skull fracture. In all cases there were two or more indications of increased intracranial pressure. Only the readings of the patients who were able to coöperate and remain quiet for the duration of the examination were used for the study. The technique employed was as follows: The patient was placed on his side and made as comfortable as possible without a sedative. After the spinal puncture needle had been inserted between the second and third lumbar vertebrae, with as little loss of cerebrospinal fluid as possible, a water manometer was connected with the needle and held in place for the duration of the test. As soon as a constant cerebrospinal fluid pressure was obtained, from 50 to 100 cc. of a 50% dextrose solution was injected slowly into the vein. Manometer readings were taken every 5 seconds for 5 minutes and every 15 seconds thereafter for periods up to 2 hours in length. Blood pressure readings were taken throughout the examination. No other method of dehydration was used either before or during the examination.

Results. The results of this study are shown in the accompanying table. The data show that in only one case was the cerebrospinal fluid pressure reduced by the intravenous injection of 50% dextrose solution, without reaching, at some time during the experiment, a higher level than that of the original pressure. In one other case

there was an initial fall followed by a rise and in 7 cases there were initial rises in pressure. Subsequent falls in pressure were observed in some of these but secondary rises brought the pressure at the end of the experiment to a higher level than was observed before the injection of the dextrose solution. In only one case was the pressure lower at the end than at the beginning of the examination.

My explanation of these variations in cerebro-spinal fluid pressure is that this pressure is elevated by the oxidation of the injected dextrose solution which draws the fluid from the body tissues and releases it by osmosis to the circulation. As more fluid is drawn into the circulation, the cerebro-spinal fluid pressure increases, and *vice versa*.

These studies show that in cases of brain tumor the results of the intravenous injection of hypertonic dextrose solution upon the pressure of the cerebro-spinal fluid are variable. The method may be tried in cases in which a rapid drop in pressure is desired but such a result cannot be assured. This procedure should be supplemented by other clinical methods of dehydration such as limitation of fluids by mouth and the purging use of magnesium sulphate either by mouth or by enema.

Conclusions. 1. The intravenous injection of hypertonic dextrose solution in cases of brain tumor sometimes reduces the cerebro-spinal fluid pressure temporarily within the first 2 hours after injection; in most cases it causes an increase in pressure at some time during this period.

2. The intravenous injection of saturated dextrose solution cannot be depended upon, in itself, to reduce the cerebro-spinal fluid pressure in cases of brain tumor.

* BIBLIOGRAPHY

- (1.) Cushing, H., and Foley, F. E. B.: *Proc. Soc. Exp. Biol. and Med.*, 17, 217, 1920. (2.) Faivre, E.: *Des granulations méningiennes*, Thèse de Paris, 1853. (3.) Fay, T.: *J. Am. Med. Assn.*, 84, 1261, 1925; *Ann. Surg.*, 101, 76, 1935. (4.) Foley, F. E. B., and Putnam, T. J.: *Am. J. Physiol.*, 53, 161, 1920. (5.) Forbes, H. S., Fremont-Smith, F., and Wolff, H. G.: *Arch. Neurol. and Psychiat.*, 19, 73, 1928. (6.) Gamble, J. L.: *New England J. Med.*, 201, 909, 1929. (7.) Grant, F. C.: *The Value of Hypertonic Solutions by Mouth, by Rectum or by Intravenous Injection for the Reduction of Increased Intracranial Pressure*, Chap. 28 in *Intracranial Pressure in Health and Disease*, vol. 8, Baltimore, The Williams & Williams Company, 1929. (8.) Hassin, G. B.: *Arch. Neurol. and Psychiat.*, 20, 1172, 1928. (9.) Jackson, H., Kutsunai, T., Leader, L. O., and Joseph, L. D.: *J. Am. Med. Assn.*, 100, 731, 1933. (10.) Kappers, C. V. A., Huber, G. C., and Crosby, E. C.: *The Comparative Anatomy of the Nervous System of Vertebrates Including Man*, The Macmillan Company, New York, 1936. (11.) Key, E. A. H., and Retzius, G.: *Studien in der Anatomie des Nervensystems und des Bindegewebes*, Samson and Wallin, Stockholm, 1875-1876. (12.) Kubie, L. S., and Hetler, D. M.: *Arch. Neurol. and Psychiat.*, 20, 749, 1928. (13.) Kubie, L. S.: *Ibid.*, 16, 319, 1926. (14.) Magendie, F.: *Recherches physiologiques et cliniques sur le liquide céphalo-rachidien ou cerebro-spinal*, Mequignon-Marvey, fils, Paris, 1842. (15.) Masserman, J. H.: *J. Am. Med. Assn.*, 102, 2084, 1934. (16.) Masserman, J. H., and Schaller, W. F.: *Arch. Neurol. and Psychiat.*, 30, 107, 1933. (17.) Merritt, H. H.: *Ibid.*, 34, 1175, 1935. (18.) Milles, G., and Hurwitz, P.: *Arch. Surg.*, 24, 591, 1932. (19.) Wood, L. H.: *J. Med. Res.*, 26, 21 and 51, 1914-1915. (20.) Wood, L. H., and McKibben, P. S.: *Am. J. Physiol.*, 48, 512, 1919. (21.) Wolff, H. G., and Forbes, H. S.: *Arch. Neurol. and Psychiat.*, 20, 73, 1928.

VASODEPRESSOR ACTIVITY OF BLOOD OF NORMAL AND BURNED DOGS. CRITICISM OF METHOD.

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PROOF of the existence of appreciable quantities of blood histamine in normal animals has rested upon: 1, a few chemical analyses, and, 2, the production by blood extracts of characteristic effects on isolated tissues and of vasodepression in the cat.

In addition to the foregoing methods, in burned animals, blood and tissue extracts have been injected into normal animals and the resulting symptoms observed. For the actual extraction of histamine from tissues, various methods have been used.

Reports have varied widely concerning the quantity of histamine in blood. Koessler and Hanke⁵ and Phemister and Handy⁶ found no histamine definitely present in blood; while Harris,⁴ Best and McHenry,^{2a} and Barsoun and Gaddum¹ found it present in appreciable quantities.

Pharmacologic assay of tissue histamine is especially difficult because substances such as peptone, acid hydrolysis products of protein, choline, acetylcholine, adenylic acid and related compounds—either initially present or else formed during the preparation of the assay solution—also lower the blood pressure of the assay animal.

In view of the difficulty of extracting tissue histamine and because of the vasodepressor action of the various substances present in the extracts, it was deemed advisable to examine critically the extraction method most commonly used.

Experimental. The assay solution of normal dog's blood, as well as a sample of the cat's own blood and an egg albumen solution, was prepared by the method of Best and McHenry.^{2a} Ether was not used to anesthetize the assay cat, because of the difficulty in maintaining even anesthesia throughout the experiment. Instead, sodium pentobarbital, 28.6 mg. per kilo of body weight, was injected intravenously.

In the assay, precautions pointed out by Burn^{3a, b} were observed. The assay solution (not more than 2 cc. per kilo of body weight) was injected into the femoral vein. Blood pressure, period of injection, and time in seconds were recorded. Injections were not repeated within 5 minutes. In each case the blood pressure was allowed to approximate its initial level. Exact quantities of histamine acid phosphate were injected to give a fall in blood pressure comparable to that produced by the assay solution.

The vagi were paralyzed with atropine sulphate and then stimulated by an induced current to prove the effectiveness of the atropinization.

The assay solution was again injected. If vasodepression resulted, then pure histamine was injected intravenously in a quantity sufficient to lower the blood pressure to the same extent.

TABLE I

B. P. before injection (mm.),	Latent period (sec.)	Primary fall (mm.)	Time to maximum fall (sec.)	Maximum fall (mm.)	Time to recovery (sec.)	Recovery (mm.)
108	5.0	108	0	0	20	10
109	5.0	109	0	0	20	10.5
128	6.0	140	0	0	20	10.5
170	13.0	183	174	16.5	113	15
118	20.0	118	118*	118	25	15.5
191	26.0	194	182	183	20.0	20.5
112	20.0	120	112*	112	20	10.5
154	22.0	178	148	148	20	11.5
120	24.0	130	120*	120	20	11.5
161	13.0	180	164	164	20	15
108	25.0	122	80	120	20	15.5

* Primary fall eliminated by atropine.

Solutions:

H6—Histamine, 0.01 mg. per kilo before atropine, H6A—same after atropine, H6A—0.01 mg. (after atropine).

U1—Extract of egg albumen (0.032 gm.) before atropine, U1A—same after atropine.

GG1—Normal dog's blood extract (0.25 cc.) before atropine, GG1A—same after atropine.

HH1—Burned dog's blood extract (0.32 cc.) before atropine, HH1A—same after atropine.

VI—Cat's own blood extract (0.31 cc.) before atropine, V1A—same after atropine.

Assay solutions of blood from burned dogs showed little quantitative, and no qualitative, differences in blood pressure effect from those of the same dog before burning.

The albumin extract solution produced the same type of fall as the assay solution prepared from blood. The cat's own blood, prepared in the same manner as dog's blood, produced a marked vaso-depression, very similar to that of the dog's blood assay solution.

Data shown in Table I are representative of the results obtained in all the assays. Histamine, 0.01 mg. per kilo, caused a fall in blood pressure beginning in 5 seconds and reaching 42 mm. Before atropinization, the assay solution of normal dog's blood caused a fall in blood pressure of 90 mm., beginning 26 seconds after injection. After atropinization, the same solution caused a fall of only 20 mm. beginning in 20 seconds.

The assay solution of blood from burned dogs, before atropinization, produced a fall of 68 mm., beginning 22 seconds after injection. After atropinization, the same sample produced a fall of 32 mm., beginning in 24 seconds. The albumen extract before atropinization produced a primary fall of 16 mm. with a latent period of 6 seconds and maximum fall of 66 mm. after 13 seconds, whereas the same extract, after atropinization, caused a fall of 28 mm., with a latent

period of 26 seconds. The assay solution of the cat's own blood, before atropinization, produced a primary fall of 40 mm. and a maximum fall of 106 mm. with a latent period of 13 seconds. After atropinization, the maximum fall was 30 mm.

Discussion. Best and McHenry^{2b} have stated that "the inference that histamine is present is legitimate if the results of a complete physiologic analysis of a solution are identical to those obtained with pure histamine." It is evident that histamine is not responsible for the vasodepression produced by these assay solutions. The long latent period suggests that the vasodepressor substance was formed or liberated in the test animal from the solution injected, and was not present as such in the solution. This long latent period alone is sufficient to eliminate histamine as the cause of the fall in blood pressure.

Additional evidence that histamine is not the responsible factor is furnished by the changed effect following atropine. Furthermore, the curve produced by the assay solution is different in appearance from that produced by histamine in doses sufficient to give a comparable fall in blood pressure. Again, if histamine were the responsible factor, the cat's own blood should not contain sufficient histamine to produce vasodepression when prepared as a diluted assay solution.

Assay solutions of the blood of burned dogs, in most instances, produced no greater vasodepression than assay solutions of normal dog's blood. In those instances in which the fall was greater, the increased fall may be explained by the concentration of blood with concentration of blood protein due to fluid loss in the burned animal.

Protein is the common factor in the substances prepared as assay solutions. Since acid hydrolysis can occur during the preparation, the substance, or substances, responsible for the fall is possibly a product of the protein hydrolysis. Vaughan⁷ showed that such protein split products may bring about vasodepression.

Summary. 1. The fall in blood pressure, caused by assay solutions prepared from blood of normal and burned dogs by the Best and McHenry method, is not due to histamine.

2. The increased vasodepression produced by assay solutions of blood of dogs following burns is accounted for by the increased blood protein concentration due to fluid loss.

3. The vasodepressor action of the solutions is possibly caused by a protein split product formed from blood protein during the preparation of the assay solution.

REFERENCES.

- (1.) Barsoum, G. S., and Gaddum, J. H.: *J. Physiol.*, 85, 1, 1935.
- (2.) Best, C. H., and McHenry, E. W.: (a) *Ibid.*, 70, 349, 1930; (b) *Physiol. Rev.*, 11, 371, 1931.
- (3.) Burn, J. H.: (a) *Methods of Biological Assay*, New York, Oxford University Press, 1928; (b) *Physiol. Rev.*, 10, 146, 1930.
- (4.) Harris, K. E.: *Heart*, 14, 161, 1927.
- (5.) Koessler, K., and Hanke, M. T.: *J. Biol. Chem.*, 59, 879, 1924.
- (6.) Phemister, D. B., and Handy, J.: *J. Physiol.*, 64, 155, 1927.
- (7.) Vaughan, V. C., Vaughan, V. C., Jr., and Vaughan, J. W.: *Protein Split Products in Relation to Immunity and Disease*, Philadelphia, Lea & Febiger, 1913.

BOOK REVIEWS AND NOTICES.

HISTORY OF CHINESE MEDICINE. Being a Chronicle of Medical Happenings in China from Ancient Times to the Present Period. By K. CHEN WONG, Licentiate of Medicine and Surgery, Hongkong, etc., and WU LUN-TSU, M.A., M.D. (CANTON), D.L.M.S. (TORONTO), HON. LUN-D. (PEKING), LL.D., Sc.D., C.P.H., Director, National Quarantine Service, etc. Pp. 996; illustrated. Second Edition. Shanghai: National Quarantine Service, 1936. Price, \$9.00.

AIMING to compose a history both of the theory and practice of the twice-honored native art" of China, and home and abroad Chinese progress in modern medical science, the authors have really produced 2 books that necessarily vary greatly in content and form of treatment, even though it is maintained that Chinese medicine to be appreciated must be studied as one whole. The first quarter of the volume, by the medical historian, K. C. Wong, presents a panorama from "mythical times up to the close of the 18th century"; while the larger portion by Wu Lun-Tsu, gives more considerable detail an account of the progress in China of occidental medicine in the past 230 years. One rather unfortunate sign of this intention, the appearance at the end of Book I of a chronological table that runs to A.D. 1887 with a second table at the end of Book II beginning with 1893. Significant of the form of treatment is that the first of the 2 tables occupies 31 pages, the latter 37. In the middle of the volume, too, are found useful bits of the Chinese dynasties and of important Chinese medical books.

To the ordinary reader, Book I will doubtless prove the more attractive. The most ancient of existing civilizations, China had her minstrel "celebrating her ancient heroes, whose tombs had already been with them for nearly 13 centuries," when in Europe our first poet "Omer smote 'i-bloomin' lyre." Starting with Yu Hsi, the legendary founder of the Chinese nation who lived about 2600 B.C., recorded Chinese medicine begins with his Pa Kua (Eight Diagrams), on which was founded Chinese medical philosophy, including the famous Yang and Yin (male and female) principles. The second of the mythical medical trinity, Shen Nung, is said by Wong and Wu to have reigned from 2838-2698 B.C., a truly heroic assignment that is less acceptable than Morse's figures, 2767-2687. Especially a student of drugs and poisons, Shen was known as the Father of Medicine and is still worshipped by the native drug dealers as their patron god. To Huang Ti, the 3d member of the Trinity, born the year of Shen Nung's death, is ascribed, with dubious historical support, the *Nei Ching* (Internal Classic), the earliest and greatest of Chinese medical writings. In its 2 books are outlined the paths that Chinese medicine was to follow for 4½ millennia: Most important features are the workings of Yin and Yang, the five elements, the functions of the five viscera, the varieties of the Pulse and their significance, the principles, use and contraindication of Acupuncture, Fevers, Bloodletting. The book's already sophisticated subtleties were not a little complicated by the 49 commentaries that appeared of various intervals during the dynastic period. A high point in Chinese medicine was the Chou dynasty (1121-249 B.C.), the age of Confucius, Mencius and Lao Tse, especially productive in the fields of medical organization, hygiene and public health. Another was the Han dynasty (B.C. 206-A.D. 220), in which appear 3 of the greatest names of Chinese medicine, Ts'ang Kung, Chang Chung Ching and Hua T'o (the Chinese Hippocrates), the father of surgery and discoverer of anesthesia (an effervescent powder). These and the trinity previously mentioned constitute the chief gods of medicine in China today. In the T'ang dynasty (618-907) Chinese medicine is said to have reached its zenith. Seven specialties were recognized, and 4 kinds of doctors (physicians, acupuncturists, masseurs, and

exorcists). Drugs were divided into 10 main classes according to their action. Progress was still possible, though necrotizing rigidity had begun. Especially in the last 2 dynasties (Ming and Ch'ing) is the sterile decline apparent. Medical schools vanished, except for the one at Peking, and this was restricted to training the physicians for the Imperial family. Literally, any one could put up a sign and practice and there was no government supervision. Even the literati became subdivided into many cliques and exerted less and less influence in the country at large. Dr. Wong is able to add many life-giving details to this bare skeleton. Interesting accounts of the opium evil and of castration (including amputation of the penis) are found in the sections on cultural conditions and on surgery. Among the famous ancient drugs described are accounts of ginseng, chaulmoogra oil and ephedrine.

The story of smallpox prophylaxis is divided between both books—the use of inoculation about 1000 A.D. (Sung dynasty) appearing in Book I; while to vaccination introduced by Alex Pearson within a few years of Jenner's discovery is given a whole chapter in Book II.

The first book inevitably invites comparison with Morse's volume in the *Clio Medica* series, which though much smaller covers the same period. In the comparison neither suffers, as both are obviously written by men thoroughly conversant with their subject. The same topics are regarded as fundamental by both and facts are rarely contradictory. The Yang and Yin theory, the Gods of Medicine and acupuncture may be treated at greater length in the *Clio* volume; but this is more than counterbalanced by the more detailed treatment that the bigger volume permits of such topics as ancient medical drugs, medicine under the various dynasties, the early history of leprosy, beri-beri, cholera, smallpox and syphilis. Both books carry illustrations of the important medical Gods, both from authentic sources and yet as different as black is from white.

This Book I paints an interesting and instructive picture; yet, as the author points out, we must agree with Mencius, "It is better not to have the *Book of History* if we believe everything in it."

Dr. Wu's book on the "Introduction and Development of Modern Medicine in China" not only should serve its purpose of demonstrating to students of the old school that medical science "has not remained stationary since the time of Hua T'o"; but also forms a permanent and extremely valuable, detailed record of the various steps by which modern medicine gained its foothold in this most conservative of countries. The form of treatment is mostly chronological, 11 of the 15 chapters being given to the periods between 1820 and 1927. For each period, and some do not exceed 5 years, leading attributes are selected, such as: Introduction of western methods, progress in medical education, the spread of bubonic plague in 1894, and pneumonic plague in 1910, public health work, foundation of hospitals and medical schools, medical journals (both in Chinese and foreign languages), and the final period (1928–1936), consolidation under government auspices (98 pages).

The distinguished author, now head of the National Quarantine Service, is pardonably, and we hope legitimately, proud of the great advances made in public health, especially since the establishment of a National Ministry of Health in 1928. Grateful for the stimulus and actual help that has come from outside, he properly emphasizes the predominant achievement of the Chinese themselves. Though recognizing the vast fields still to be conquered (China, for instance, has 800,000 persons per hospital as against India's 42,700, Japan's 33,500, and the United States' 18,171), Chinese leaders are not sacrificing quality to quantity and are confidently proceeding with their policy of intensive medical progress. The activities are by no means limited to the coastal centers with which foreigners are familiar: Rural and county health centers have been established in 10 of the score or more of Chinese provinces, midwifery schools in 11, leprosaria in 11, over

6000 modern trained physicians are known to be spread over 10 provinces, while 426 hospitals were listed in 1934 in 20 provinces. Yet we may not forget that this is China; on page 448 we read: "Yuan crowned himself Emperor on December 13, 1915, but owing to growing opposition, fell sick and died in 100 days."

Statistics furnish tedious reading; yet one cannot have such a documented, detailed record as this without them; also the mass of detail included has necessarily resulted in a presentation rather than a narrative. For the very casual reader who does not wish even to browse through the text, the final chapter will summarize what it is all about. For the historical student, whether of the romantic, far distant past or of the active present, the whole volume will serve as a treasure house of reliable information. The new spirit of China, exemplified for the author in Sun Yat Sen and the Kuomintang, certainly appears to have achieved noteworthy progress in the field of health. Let us hope that it will be preserved by a similar progress along political lines!

We have devoted an unusually large space to this review both because the first edition was not "noticed" in this department and to demonstrate the importance of a work that must remain for a long time the classic in its field.

E. K.

THE STORY OF LIVING THINGS. A Short Account of the Evolution of the Biological Sciences. By CHARLES SINGER. Pp. 572; 194 illustrations. New York: Harper & Brothers, 1931. Price, \$3.00.

Two points stand out in this book: first, that though he is a historian, the author, like Ovid, rejoices in his own times and utilizes the past to illuminate the present; and second, that in spite of the progress of biologic specialization, it is possible to include within a book of medium size a scholarly and mature consideration of the problems of biology as a whole. Far different from the ordinary Introduction to Biology, this book achieves an adequate critical survey in simple concise terms, because, as the author himself suggests, "It is not the positive conquests of science that are peculiarly obscure, but rather the confused yet active battle-front along which science is advancing at any given moment."

The arrangement of the book is semi-chronologic. Part I carries the story of Biology from Aristotle through Harvey. Part II lays the basis for modern biology in sections on Inductive Philosophy, Classificatory Systems, Comparative Methods (*Naturphilosophie*), geographical and geological distribution, and evolution. The final Part selects 7 topics as the main themes of contemporary biology: the Cell, Vital Activity, Relativity of Functions, Biogenesis, Ontogenesis, Sex, Heredity.

Dr. Singer's fitness for such a task is unquestioned. Again he has demonstrated not only his familiarity with the various branches of biological science; but, much more, his ability to penetrate to the kernel of the matter, evolve thought-stimulating sequences and present a story sufficiently simple and leavened with personalities to carry along the serious reader entertainingly as well as profitably.

E. K.

AN INTRODUCTION TO PSYCHOLOGICAL MEDICINE. By R. G. GORDON, M.D., D.Sc., F.R.C.P. (Ed.), Physician to Royal United Hospital, Bath; Physician to Bath and Wessex Orthopaedic Hospital, Bath, etc., N. G. HARRIS, M.D., B.S. (Lond.), D.P.M., Physician in Charge to Woodside Hospital; Physician for Psychological Medicine, Middlesex Hospital, etc., and J. R. REES, M.A., M.D., D.P.H. (Camb.), Medical Director, Institute of Medical Psychology. Pp. 386; illustrated. New York: Oxford University Press, 1936. Price, \$4.00.

WRITTEN as a text-book for the use of medical students, this work on psychiatry has certain interesting and commendable features. The first

70 pages are devoted to a brief survey of the field of psychology, especially in its relation to psychiatry. The workings of the diseased mind are the better appreciated by him who also has an understanding of the functioning of the normal mind, a knowledge of psychology which most texts in psychiatry take for granted. The next 60 pages take up the general principles of psychopathology and the psychopathology of common symptoms; this section is particularly well handled. Then follow the descriptions of the various mental disorders, with sections on the psychoneuroses, the psychoses, mental deficiency. The last two have valuable discussions of the legal aspects and the laws (British) relating to mental disorders. Since the treatment of mental illness is a subject for postgraduate study, no details of elaborate psychotherapeutic measures have been included, but the principles of treatment are adequately given. The presentation of the material is sound and the book is well written.

R. K.

PATHOLOGIE DER FUNKTIONEN UND REGULATIONEN. By PROF. DR. L. LICHTWITZ, Chef der medizinischen Abteilung des Montefiore Hospital, New York; Clinical Professor of Medicine, Columbia University, New York. Pp. 332; 65 illustrations and 61 charts. Leyden: A. W. Sijthoff's Uitgeversmaatschappij, N.V., 1936. Price, Paper, holl. fl. 13.25; Bound, holl. fl. 14.50.

THESE essays by a distinguished internist cover a wide range of medical interests. They deal particularly with the disorders of internal secretion and the part played by the autonomic nerve system in the regulation and integration of the functions of the several organs in health and in disease. As the author himself states his is not a textbook or a work of reference but rather an illustration, through the discussion of many examples, of a particular mode of thought and method of investigation. There are chapters on the vegetative system and on general endocrinology, on the regulation of blood sugar and on hypoglycemia, on renal diabetes, on the pathology of the defense mechanism (inflammatory and immune reactions), on water metabolism, diseases of the joints and of the skeleton, on gout, on disturbance fat metabolism, on function and destruction of erythrocytes, diseases of the blood, hypertension, angiospastic diseases, visceral neuroses, functional pathology of the liver, nephritis, nephrosis, and the kidney of pregnancy, on age and senescence. All of these are worth reading, for they reflect the studies and experience of a medical investigator who obviously is both an optimist and a skeptic, qualities which the author believes should be among the chief characteristics of the physician. The excellent photographs, many of them of patients, add much to the value and enjoyment of this book.

B. L.

ELECTRICAL SIGNS OF NERVOUS ACTIVITY. By JOSEPH ERLANGER, Professor of Physiology, Washington University, and HERBERT S. GASSER, Director, The Rockefeller Institute for Medical Research. Pp. 221; 113 illustrations. Philadelphia: University of Pennsylvania Press. London: Humphrey Milford; Oxford University Press, 1937. Price, \$3.50.

THE present monograph embodies the third series of lectures delivered under the auspices of the Johnson Foundation for Research in Medical Physics. Like its immediate predecessor "it bears witness to the influence that developments in the fundamental sciences exert upon trends and progress in physiology. For it will become evident that but for contributions made by physicists in the field of vacuum-tube methods, which in turn rest upon experiments still more fundamental, on the theory and the production of electromagnetic waves, neither of these series of lectures would have

been possible." The studies discussed deal with: The analysis of the compound action potential of nerve; the comparative physiological characteristics of nerve fibers; some reactions of nerve fibers to electrical stimulation; sequence of potential changes; the excitability cycle. The lectures have admirably succeeded in demonstrating the applicability of physical methods to biological and medical problems. If for no other reason, the general medical reader will find this monograph of great interest; for the modern student of neurology the narrative of achievements, which would have been impossible but a few years ago, will be a source of inspiration and stimulation to "go and do likewise."

B. L.

NEW BOOKS.

Clinical Parasitology. By CHARLES FRANKLIN CRAIG, M.D., M.A. (Hon.), F.A.C.S., F.A.C.P., Col. U. S. Army (Retired), D.S.M., Professor of Tropical Medicine in the Tulane University of Louisiana, New Orleans, and ERNEST CARROLL FAUST, M.A., Ph.D., Professor of Parasitology in the Department of Tropical Medicine, Tulane University of Louisiana, New Orleans. Pp. 733; 243 illustrations. Philadelphia: Lea & Febiger, 1937. Price, \$8.50.

Clinical Allergy. By LOUIS TUFT, M.D., Chief of Clinic of Allergy and Applied Immunology, Temple University Hospital; Associate in Immunology, Temple University School of Medicine; Director of Laboratories, Pennsylvania Department of Health, Philadelphia. Introduction by JOHN A. KOLMER, M.D., Dr.P.H., D.Sc., LL.D., L.H.D., Professor of Medicine, Temple University; Director of Research, Institute of Cutaneous Medicine, Philadelphia. Pp. 711; 82 illustrations. Philadelphia: W. B. Saunders Company, 1937. Price, \$8.00.

The Principles and Practice of Clinical Psychiatry. By MORRIS BRAUDE, M.D., Associate Clinical Professor of Psychiatry, Rush Medical College, The University of Chicago; Attending Psychiatrist, Cook County Psychopathic Hospital, Chicago. Pp. 382; 7 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, \$4.00.

A Brief Rule to Guide the Common-people of New England How to Order Themselves and Theirs in the Small Pocks, or Measels. [First published in 1677/8, reprinted in 1702 and 1721-22.] By THOMAS THACHER. Facsimile Reproductions of the Three Known Editions with an Introductory Note by HENRY R. VIETS, M.D. Pp. 54; illustrated. Price, \$1.50.

A Discourse upon the Institution of Medical Schools in America. [Reprinted from the first edition, Philadelphia, 1765.] By JOHN MORGAN. With an Introduction by ABRAHAM FLEXNER. Pp. 63; 1 illustration. Price, \$2.00.

Adaptation in Pathological Processes. [Reprinted from Transactions of the Congress of American Physicians and Surgeons, 1879, fol. IV, pp. 284-310.] By WILLIAM H. WELCH, M.D., LL.D. With an Introduction by Dr. SIMON FLEXNER. Pp. 58; 1 illustration. Price, \$1.50.

The above 3 books, (Publications of the Institute of the History of Medicine, The Johns Hopkins University, Fourth Series, Bibliotheca Medica Americana, Vols. I, II, and III, respectively.) Baltimore: The Johns Hopkins Press, 1937.

The Cost of Adequate Medical Care. By SAMUEL BRADBURY, M.D. Pp. 86; 13 tables. Chicago: The University of Chicago Press, 1937. Price, \$1.00.

Obstetric and Gynecologic Nursing. By FREDERICK H. FALLS, M.S., M.D., F.A.C.S., Professor of Obstetrics and Gynecology, University of Illinois,

College of Medicine; Attending Gynecologist of the Illinois Research and Educational and Cook County Hospitals, etc., and JANE R. McLAUGHLIN, B.A., R.N., Supervisor of the Department of Obstetrics and Gynecology, Research and Educational Hospital, University of Illinois, College of Medicine; Instructor in Department of Obstetrics, University of Illinois, College of Medicine. Pp. 492; 83 illustrations (by Charlotte S. Holt). St. Louis: The C. V. Mosby Company, 1937. Price, \$3.00.

Induced Inflammation of the Nasal Mucosa as Preparation for the Experimental Active Immunization Against Poliomyelitis Virus. By S. PESKIND, B.S., M.D., Cleveland, Ohio. Pp. 8. Cleveland: S. P. Mount Printing Company, 1937. (Price not given.)

Clinical Endocrinology. By SAMUEL A. LOEWENBURG, M.D., F.A.C.P., Clinical Professor of Medicine, Jefferson Medical College, Philadelphia; Assistant Visiting Physician, Philadelphia General and North Liberties Hospitals, and Eagleville Sanatorium for Consumptives, etc. Foreword by HOBART A. REIMANN, M.D., Professor of Medicine and Clinical Medicine, Jefferson Medical College, Philadelphia. Pp. 825; 184 illustrations, 37 charts and tables. Philadelphia: F. A. Davis Company, 1937. Price, \$8.00.

The Traffic in Health. By CHARLES SOLOMON, M.D., Assistant Clinical Professor of Medicine, Long Island College of Medicine; Lecturer in Materia Medica, Training School for Nurses, Jewish Hospital of Brooklyn. Pp. 393. New York: Navarre Publishing Company, 1937. Price, \$2.75.

Condition Satisfactory. A Physician's Report of His Own Illness. By DR. SÁNDOR PUDER. Translated from the German by HILDEGARD NAGEL. With a Foreword by FRIGYES KARINTHY. Pp. 201. New York: ALFRED A. KNOPF, 1937. Price, \$2.00.

The Harvey Lectures, Series XXXII. Delivered under the Auspices of The Harvey Society of New York, 1936-1937. Under the Patronage of the New York Academy of Medicine. By DRS. WILDER PENFIELD, EUGENE M. LANDIS, W. WALTER RANSON, R. SCHOENHEIMER, THORVALD MADSEN, HERBERT S. GASSER, C. N. H. LONG and SIR HENRY DALE. Pp. 245; illustrated. Baltimore: The Williams & Wilkins Company, 1937.

The usual high standard of this publication is maintained in the present volume by the following authorities: W. Penfield, "The Cerebral Cortex and Consciousness;" E. M. Landis, "The Passage of Fluid through the Capillary Wall;" S. W. Ranson, "Some Functions of the Hypothalamus;" R. Schoenheimer, "The Investigation of Intermediary Metabolism with the Aid of Heavy Hydrogen;" T. Madsen, "The Scientific Work of the Health Organization of the League of Nations;" H. S. Gasser, "The Control of Excitation in the Nervous System;" C. N. H. Long, "The Influence of the Pituitary and Adrenal Glands upon Pancreatic Diabetes;" Sir H. Dale, "Transmission of Nervous Effects by Acetylcholine."

E. K.

Tumors of the Nervous System. An Investigation of the Most Recent Advances. The Proceedings of the Association, New York, December 27 and 28, 1935. (Association for Research in Nervous and Mental Disease, Vol. XVI of a Series of Research Publications.) Editorial Board: EDWIN G. ZABRISKIE, ANGUS M. FRANTZ, CLARENCE C. HARE. Pp. 394; 213 illustrations and 64 tables. Baltimore: The Williams & Wilkins Company, 1937. Price, \$7.50.

The Medical Clinics of North America, Vol. 21, No. 4 (Philadelphia Number, July, 1937). Pp. 315; 11 illustrations. Philadelphia: W. B. Saunders Company, 1937.

In this Philadelphia number, the most important feature is the 9-article symposium on cardiovascular disease. The 14 other articles range from the recondite essential pentosuria to the (*horribile dictu*) "acute abdomen." As usual, much sound clinical information is to be found within the covers of this number.

E. K.

Diseases of the Nervous System in Infancy, Childhood and Adolescence. By FRANK R. FORD, M.D., Associate Professor of Neurology, The Johns Hopkins University. Pp. 953; 107 illustrations, 14 charts and 14 tables. Springfield, Ill.: Charles C Thomas, 1937. Price, \$8.50.

NEW EDITIONS.

An Introduction to Dermatology. By RICHARD L. SUTTON, M.D., Sc.D., LL.D., F.R.S. (EDIN.), Professor of Dermatology, University of Kansas School of Medicine, and RICHARD L. SUTTON, JR., A.M., M.D., L.R.C.P. (EDIN.), Instructor in Dermatology, University of Kansas School of Medicine. Pp. 666; 229 illustrations. Third Edition. St. Louis: The C. V. Mosby Company, 1937. Price, \$5.00.

The third edition of Sutton and Sutton has been expanded by 45 new illustrations and brief descriptions of 35 previously undiscussed dermatoses. Hence it emerges as an increasingly authoritative and valuable guide to present day dermatology for the practitioner and medical student. An attempt at reclassification has been made in keeping with the newer etiologic and functional viewpoint in dermatology. One misses a bibliography, although much of the pertinent literature is well covered in the discussion. The book can be thoroughly recommended as an up to date, readable and highly practical presentation of the subject. V. G.

Manual of the Diseases of the Eye for Students and General Practitioners. By CHARLES H. MAY, M.D., Consulting Ophthalmologist to Bellevue, Mt. Sinai and French Hospitals, New York, etc. Pp. 498; 376 illustrations including 26 plates with 78 colored figures. Fifth Edition, revised with the assistance of CHARLES A. PERERA, M.D., Instructor in Ophthalmology, College of Physicians and Surgeons, Medical Department of Columbia University, New York. Baltimore: William Wood & Co., 1937. Price, \$4.00.

This excellent manual continues to be the most popular text for medical students in their course in ophthalmology. The fifteenth edition has been carefully and thoroughly revised and brought up to date to include such recent subjects as dinitrophenol cataract, inclusion body conjunctivitis, gonioscopy, polaroid glasses, etc. F. A.

Treatment by Diet. By CLIFFORD J. BARBORKA, B.S., M.S., M.D., D.Sc., F.A.C.P., Department of Medicine, Northwestern University Medical School, Chicago. Pp. 642; 8 illustrations. Third Edition, revised. Philadelphia: J. B. Lippincott Company, 1937. Price, \$5.00.

Rose and Carless Manual of Surgery. American Fifteenth Edition Edited by WILLIAM T. COUGHLIN, B.S., M.D., F.A.C.S., Professor of Surgery and Director of the Department of Surgery, St. Louis University School of Medicine; Surgeon-in-Chief, St. Mary's Group of Hospitals, St. Louis. From the Fifteenth English Edition by CECIL P. G. WAKELEY, D.Sc. (LOND.), F.R.C.S. (ENG.), F.R.S. (EDIN.), Senior Surgeon, King's College Hospital, etc., and JOHN B. HUNTER, M.C., M.CHIR. (CANTAB.), F.R.C.S. (ENG.), Surgeon, King's College Hospital, etc. Pp. 1586; 900 illustrations and 26 plates (18 in color). Baltimore: William Wood & Co., 1937. Price, \$9.00.

Disorders of the Blood. Diagnosis, Pathology, Treatment and Technique. By LIONEL E. H. WHITBY, G.V.O., M.C., M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), D.P.H., Assistant Pathologist, The Bland-Sutton Institute of Pathology, The Middlesex Hospital, and Pathologist, The Children's Hospital, Hampstead, and C. J. C. BRITTON, M.D. (NEW ZEALAND), D.P.H., Assistant Pathologist, The Bland-Sutton Institute of Pathology, The Middlesex Hospital; Late Assistant Pathologist, Christchurch Hospital, New Zealand. Pp. 582; 60 illustrations, 12 plates (8 colored), and 15 tables. Second Edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, \$7.50 with washable cloth cover.

PROGRESS OF MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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HYSTERECTOMY.

FOR many years there have been discussions among gynecologists relative to the type of operation which should be performed in a patient in whom removal of the uterus is indicated. The aspects of the question which are most frequently argued are: 1, should the abdominal or the vaginal route be employed? 2, if the abdominal route is selected, should the operation consist of removal of the entire uterus or only the supracervical portion, commonly called the subtotal or supravaginal operation? 3, should the ovaries be retained or removed in the cases where they appear grossly normal? 4, in the cases where the cervix is not removed, what is the danger of the later development of cancer in this retained stump? It is not the purpose of a review of this kind to answer these questions, indeed it would be quite impossible for any reviewer to answer them to the satisfaction of everybody interested in these questions. Therefore we shall present abstracts of recent literature pertaining to the subject and allow the reader to decide on which side of the fence he prefers to be.

Abdominal Hysterectomy. In the opinion of Richardson,^{12a} the most cogent argument offered in support of the contention by the advocates of routine total hysterectomy is the apparent steadily mounting incidence of cervical stump cancer. In his own experience the occurrence of stump cancer is so rare as to be a negligible factor, but he cannot ignore the numerous reports of its occurrence in the experience of others. It is impossible to determine accurately its true incidence because no one knows how many thousands of subtotal hysterectomies have been performed throughout the world, but he does not believe that it exceeds 3%. In his opinion subtotal hysterectomy is indicated in only four types of cases: 1, those women requiring hysterectomy for benign disease who possess perfectly normal cervixes; 2, cases in which the operative hazard compels the execution of rapid and conservative surgery; 3, a few cases in which for good and sufficient reason it is of paramount importance to preserve the function of menstruation; and 4, most cases requiring hysterectomy during pregnancy. Before decid-

ing upon subtotal hysterectomy, the surgeon should scrutinize the cervix with particular care, freely utilizing such diagnostic aids as the Schiller test, colposcope and biopsy, when in doubt as to the condition of the epithelium on its surface. Furthermore, remembering how frequently coëxisting carcinoma at and above the level of the internal os is overlooked, as soon as the body of the uterus is removed by the subtotal operation, it should be laid wide open so as to permit of accurate inspection of all the endometrium; likewise all fibroid tumors should be bisected and examined and an immediate frozen section should be made of any suspicious area. He believes that there is little likelihood that stump cancer will later develop in any cervix which survives the rigid application of these tests. Although Richardson is thoroughly skilled in all types of hysterectomy and has devised a very efficient technique for the complete operation, he is unbiased and states that the complete hysterectomy is a surgical procedure of far greater magnitude, requiring larger experience and more highly developed technical skill for its successful application than does the subtotal operation.

Read and Bell¹¹ studied a series of 2344 consecutive hysterectomies at the Chelsea Hospital for Women in England which were performed for various indications by 14 gynecologists. Of this series about 75% were of the supravaginal type and 25% were total operations. In the subtotal group the morbidity was 20.6% and the mortality was 2.1%, while in the group comprising total hysterectomies the morbidity was 27.1% and the mortality was 3.1%. After carefully tabulating their studies they conclude that each of the two types of operation has a definite place in gynecologic surgery. While the morbidity and the mortality are higher for the total operation, the sequelæ following the subtotal operation are more numerous and of more serious consequence than those following the total operation. Taking into consideration the remote deaths due to these sequelæ, the remote mortality rate of the subtotal operation is appreciably raised. The majority of the remote sequelæ could have been anticipated by a more accurate investigation of the cervix before operating and by the more frequent employment of exploratory curettage to rule out malignant disease. The remote complications encountered after the subtotal operation include cervicitis, cancer of the retained stump, cervical menstruation, prolapse of the cervix, cervical fibroids and intestinal obstruction. Pulmonary embolism especially follows the subtotal operation and accounts for a considerable proportion of the deaths. The more general employment of postoperative massage and exercises might diminish the incidence of this complication. In the total operation the use of silk in the neighborhood of the vaginal vault incurs a definite risk of sinus formation. These authors do not advocate the routine use of the total operation but feel that the scope of the subtotal operation is distinctly limited, since few women who have borne children have completely healthy cervixes.

The opinion which Goodall³ expresses is based upon a personal experience arising from 550 consecutive cases of hysterectomy about equally divided between the total and the subtotal operation. As his experience improved, the totals greatly outnumbered the subtotals, so that at present the former operation is selected in about 90% of the cases. It is not his intention to force the unskilled surgeon into an

operation graver than that for which he is fitted by experience. But to the skillful surgeon, to whom a slightly longer operation presents no greater deterrent than the extra time that is expended, the total hysterectomy will present great advantages to the patient. In brief, he lists the disadvantages of the total operation as the greater time required, greater skill required, greater blood loss, greater danger to vital organs, greater difficulty if the pelvic organs are fixed deeply in the pelvic cavity or if the patients are obese. On the other hand, the advantages of the total operation are fewer immediate postoperative complications, fewer remote sequelæ and smoother recoveries. When vaginal hemorrhage occurs after the total operation, as it has in slightly over 2% of his series, the vagina should at once be cleared of clots and packed gently with gauze by means of a uterine packer. To leave the vagina filled with clots is to invite further bleeding. In every instance the above procedure, preceded by a blood transfusion, has promptly arrested the bleeding. He has found that thrombophlebitis is three times as common in the subtotal operation as in the total and he ascribes this to the fact that it is due to an infection of low virulence and in the vast majority of cases it emanates from a mucosal disease.

In a series of 1376 abdominal hysterectomies presented by Siddall and Mack,¹⁵ there were 1141 subtotal and 235 total operations with mortality rates of 2.6% and 6.4% respectively. In analyzing the series with regard to different operators with different degrees of skill, it was found that in every instance there was an advantage in mortality for the subtotal operation. Pelvic inflammatory disease made hysterectomy more dangerous and explained the higher mortality which occurred with removal of the adnexa. They believe that the danger of cancer developing in the cervical stump is not great enough to justify the additional risk of the total operation in any but a small proportion of cases. Other less dangerous procedures should be more frequently recommended. The cervix may be coned out from above at the time of the subtotal operation, but this will not remove the most frequent site of later carcinoma, namely the region of the external os. Of greater value is the removal of the cervix from below or cauterization of the cervix, either before or after the abdominal operation.

The removal of a myomatous uterus by *morcellation* is an old operation and was used to extract large growths through small incisions. The disadvantage of the procedure when practised in the orthodox manner was the increased bleeding which occurred as the tumor was delivered piecemeal. To overcome this objection Rubin¹³ has developed what he terms "retrograde" abdominal hysterectomy with avascular morcellation. The operation is like the standard hysterectomy except that the pelvic blood supply is controlled with the large uterine tumor remaining within the abdomen. After ligation of the main vessels, the tumor is removed by morcellation through a small subumbilical incision, even though the tumor mass may extend up to the xiphoid. He believes that the smaller incision will prevent large hernias and, as the uterus is allowed to occupy its natural position during the operation, it acts as a non-irritating pad which prevents the intestine from prolapsing into the wound, lessening shock. In the event that any difficulty is encountered in the course of the operation on account of the small incision, it can readily be enlarged upward as far as desired.

The operation was devised and is recommended especially for the removal of the very large fibroids.

The question of whether a hysterectomy or a more conservative method should be used for the treatment of a perforated uterus has been considered by Ernst.² He reports 34 cases of perforation of the uterus complicating induction of labor or evacuation of the uterus after abortion, with 3 deaths or 9% mortality. In this series 3 cases were treated conservatively with no mortality, 1 case was treated by simple laparotomy with drainage and died, 8 cases were treated by suture of the perforation with no mortality and in 22 cases hysterectomy was performed with 2 deaths. Two of the 3 deaths in the series were in patients who came to operation with a well-established peritonitis, in 1 of which a hysterectomy with drainage was done, while the other was so hopelessly advanced that simple drainage was all that was attempted. Therefore, of the patients who did not have peritonitis at the time of operation only 1 was lost, or a mortality of 3% which, of course, is comparatively low. Although suture of the perforation is the operation of choice in the early cases, in this series hysterectomy was indicated 20 times because of the large size of the perforation, wounds of neighboring structures, unusual thinness of the uterine wall, infection, and the like. Only 1 of these cases died and that was due to a secondary hemorrhage from the ovarian artery.

Vaginal Hysterectomy. Although the great majority of gynecologists prefer to do hysterectomy by the abdominal route, those who prefer the vaginal route are usually quite expert in its performance, and in their hands this operation has a low mortality and can be applied in many complicated cases. Heaney⁵ reports his series of 627 vaginal hysterectomies with 3 deaths, or a mortality of 0.47%. The indications for the operation were uterine fibroids in 338 cases, uncontrolled menorrhagia in 119 cases, uterine prolapse in 76, adenomyoma in 60 and for many other indications in the remainder of the series. The complication that is usually most feared is postoperative hemorrhage, but in this series there were only 5 cases. In 1 case it was necessary to perform a laparotomy and ligate a small vessel, 1 required vaginal suture, while the other 3 merely required vaginal tamponade. Adenomyoma of the rectovaginal septum is not infrequently associated with disease of the uterus requiring hysterectomy. This complication should not deter one from operating vaginally, for this growth is more amenable to attack by the vaginal route than by the abdominal. In one case of this sort a tiny perforation of the rectum was made which was immediately sutured with an uncomplicated convalescence. In 3 cases, at some time during the convalescence, the vaginal vault opened and a tube prolapsed and became adherent in the vaginal vault. In such cases the patients usually complain of a profuse watery discharge. When this occurs, slight traction is made on the tube under light anesthesia until it is completely delivered in the vagina, and then a ligature is passed around the tubal mesentery and the tube burned off with a light nasal cautery. Vaginal hysterectomy causes very little reaction to the patients, and Heaney states that there has never been reported a series of abdominal hysterectomies with so low a morbidity and mortality as he has reported in this series of vaginal operations.

The relative value of vaginal and abdominal hysterectomy for benign

uterine disease has been very ably presented by Richardson¹²⁶ without assuming a partisan attitude for either one. Major abdominal operations of any kind are not usually well borne by the aged and infirm. In this group abdominal panhysterectomy involves genuine hazard, whereas the vaginal removal of the uterus is astonishingly well tolerated. In nulliparous women whose intrapelvic ligamentous and fascial supports of the reproductive, vesical and rectal units are normal, he always performs abdominal hysterectomy, unless there exists some specific contraindication to its use. Although adequate exposure for a vaginal operation in these cases may be obtained by the use of a unilateral or bilateral Schuchardt's pararectal incision, the bleeding from these incisions is always free, and a proper reconstruction of the divided structures is not always obtained. Even with the additional exposure obtained by these incisions the hysterectomy may still be difficult and hazardous in women with deep pelvis and strong, unyielding uterine supports. Complicated pelvic lesions tremendously increase the technical difficulties. Therefore vaginal hysterectomy in the nullipara without uterine prolapse should be undertaken only by surgeons who have had large experience with the operation. As a general rule, total hysterectomy by either route should not be undertaken if there exists acute or subacute infection anywhere within the boundaries of the operative field. After the infection has subsided there are likely to be numerous adhesions which more or less fix the pelvic organs, and for this reason abdominal operation will be more satisfactory. If there are associated ovarian neoplasms it would seem wiser to employ the abdominal route so that there will be no spilling of ovarian contents and also that a thorough abdominal exploration may be made. While it is true that tumors as large as a 4 months' pregnancy can be removed by the vaginal route, it is not usually wise to do so when the tumor is larger than an 8 weeks' pregnancy. Caution should be exercised in delivering through the detached vaginal vault even a tumor of this size because of the danger of serious damage to the base of the bladder and its sphincter muscle from overstretching. If intraligamentary, retroperitoneal, cervical or subvesical myomas are to be dealt with, one should always assume that normal anatomical relationships in the true pelvis have become distorted. Frequently this occurs to an extraordinary degree and failure to recognize the added operative hazards thus produced is responsible for many divided ureters and bladder punctures. With regard to the treatment of uterine prolapse, he believes that where total hysterectomy is indicated for other reasons in conjunction with correction of the various types of vaginal hernia, the vaginal type of hysterectomy is to be preferred. He warns that operative attack upon hemorrhoids, fissure and fistula-in-ano, recto-vaginal fistula, and complete laceration of the perineum should not be combined with total hysterectomy by either route. If removal of the uterus must antedate correction of such maladies, subtotal abdominal operation is much safer, because it evades the danger of contaminating the operative field with subsequent development of serious complications and also obviates the restrictions which such operations impose upon postoperative rectal therapy. He emphasizes the importance of a thorough surgical toilet of the vulva, vagina and cervix immediately preceding the operation, and states that a total hysterectomy should

never be performed by either route in the presence of any active infection. Even in the absence of active infection the vaginal flora and the cervical glands may harbor the most virulent types of streptococci, and failure to recognize this fact is responsible for an occasional fatality and for many instances of postoperative wound infections, secondary hemorrhage, pelvic cellulitis and other complications.

Ovarian Function After Hysterectomy. Arguments have frequently been presented for and against removing apparently normal ovaries at the time of hysterectomy. The conservatives feel that even though the uterus be removed, the ovaries serve an important function in the elaboration of internal secretions of much benefit to the patient. The radical school are of the opinion that following hysterectomy the ovaries soon become almost functionless and are a source of possible future trouble and hence should be removed at the primary operation. In order to throw some light on this subject some experimental work on animals was done by Burford and Diddle.¹ They performed total hysterectomy on 5 female monkeys (*Macacus rhesus*), including mature and immature animals, and noted the effect on the ovaries. The animals were followed for periods ranging from 121 to 217 days after operation. No impairment of ovarian activity could be detected by vaginal lavage studies, "sex skin" color records, or examination of the ovaries at laparotomy. A postmortem census of the follicles in the ovaries revealed no increase in follicular atresia for either the mature or the immature group. One immature animal went on to definite sexual maturity 103 days after hysterectomy. They conclude that hysterectomy in the *Macacus rhesus* monkey is without effect upon the ovary, except for purely traumatic effects. The monkey affords no evidence that the uterus contributes any endocrine influence upon the ovary.

This subject has been studied from the clinical aspect by Marx, Catchpole and McKennon,⁷ who state that the contrast between the hormone picture and clinical symptoms after total and after subtotal hysterectomy is impressive and striking. In the majority of the total hysterectomies they observed a rapid increase in prolactin and a less rapid decrease of estrin. Hot flushes occur almost immediately following the operation. Compared with this, cases of supravaginal hysterectomy show much less violent changes of the hormone picture, occurring more gradually and in the majority of cases appearing after several years and the hot flushes occur much less frequently and much later. Among 8 cases of total hysterectomy, they found 5 manifesting hot flushes of 6 showing an increase of prolactin, whereas among 13 cases of supravaginal hysterectomy they found only 2 presenting hot flushes of 6 with a high prolactin level. These findings indicate, first, that the increase of prolactin is not necessarily associated with the production of hot flushes and, second, that with an equal rise of the prolactin level, hot flushes are more apt to occur in cases of total hysterectomy than in cases of supravaginal hysterectomy. It seems that hot flushes are more likely to develop, the more abruptly the uterine function and the normal utero-ovarian-pituitary balance are disturbed, as it occurs in the total compared with the subtotal operation. They were surprised to find how long the ovary can continue to function after supravaginal hysterectomy since they found normal quantities of estrin in 2 women,

35 and 36 years old, more than 4 and 6 years after the operation, which would contradict the opinion of previous clinical observers that the life of the ovary after hysterectomy averages only 2 years. They believe that the preservation of only a small part of the uterus seems to have a retarding effect upon the appearance of retrogressive changes in the pituitary-ovarian function and the occurrence of menopausal symptoms. Their studies seem to support the theory that the uterus elaborates a catalytic principle acting upon some part of the pituitary-ovarian hormonal mechanism, regulating its normal balance and functional harmony. The amount of estrin output after hysterectomy is determined more by the biologic quality than by the amount of ovarian tissue retained.

A similar study has been made by Tamis,¹⁶ who found that ovarian activity persisted longer in the women under 35 years of age at the time of operation than in the older group. Conservation of the ovaries in the younger group tended to retard the onset of flushes to a greater degree than in the older group, but in both groups, when they did occur, they lasted longer than when they appeared in the bilaterally oöphorectomized women. No direct relationship could be demonstrated between follicle hormone production *per se*, and the onset and severity of the vasomotor disturbances of the menopause. Whatever influence the ovary exerts over these disturbances is due to some other mechanism, in his opinion. It is believed by some that the endometrium produces a hormone and that the amount of flushes after hysterectomy is proportional to the amount of endometrial tissue excised. He therefore makes the suggestion that not only the ovaries be conserved when performing hysterectomy but also that as much of the uterine mucosa as possible be saved.

In a review of 2042 hysterectomies, Kretzschmar and Gardiner⁶ found that complete removal of all ovarian tissue hastens the onset but does not shorten the duration of symptoms of the surgical menopause, as has been previously contended. The high incidence of menopausal symptoms following operations for pelvic inflammations would suggest that conservatism in this condition is unwise, if ovarian tissue showing degenerative changes is to be retained. The onset of the surgical menopause should not presuppose a decrease in, or a cessation of, sexual activity, since 57% of the patients in this series who developed hot flashes showed either an increase or no change in their libido.

Cancer of the Cervical Stump. The most potent, if not the only reason for advising the performance of total abdominal hysterectomy, is the possibility of the occurrence of cancer in the cervical stump which remains after the supravaginal operation. As stated earlier in this review, no one knows the exact incidence of this possibility, but the figures presented by Meigs⁸ from the Massachusetts General Hospital are illuminating. There were 39,930 married women over the age of 30 admitted to the hospital wards for all reasons, from June, 1900, to June, 1933, and there were 751 patients with cancer of the cervix admitted in the same period. Thus in this population the incidence of cancer of the cervix is 1.8%. In the same 33 years there were 1774 subtotal hysterectomies for benign disease performed in the hospital, and in this period of time there were in the hospital but 13 cases of real stump cancer (0.73%). As this hospital receives patients from all

the New England states, and as many of the worst and most difficult problems reach there, it is reasonable to assume that it would admit more cancers of the cervical stump from other hospitals than it would lose following its own hysterectomies. This figure, 0.73 %, is less than one-half of the percentage incidence of cancer of the cervix. In other words, cancer of the retained cervix is not more likely after subtotal hysterectomy than, but one-half as likely as in, women as a whole. For the advocates of total hysterectomy to maintain their position it would be necessary for them to show not over a 0.73 % difference in mortality between subtotal and total hysterectomy. Meigs states that this might be accomplished by an operator well trained in this type of surgery, but to advocate total hysterectomy to all surgeons throughout the country in all patients to prevent the occurrence of cancer in the cervical stump would be the cause of far more deaths in an attempt to prevent cancer than would die of cancer itself. It is also obvious that total hysterectomy cannot be advocated in only special groups of cases, but it must be advocated in all, even those who have had no children. No one will deny that total hysterectomy is a more formidable and more serious operation than simple subtotal removal of the uterus. The morbidity, the chance of injuring the ureters and bladder, the possibility of vaginal prolapse and the foreshortening of the vagina in the young married woman are all against this operation as a routine.

In a series of 1900 cases of supravaginal hysterectomy at the Free Hospital for Women in Brookline, Pearse¹⁰ estimates that the incidence of stump cancer is about 1 %. In comparing the cases in which the operation was done for fibroids with those in which it was done for pelvic inflammatory disease, the incidence was about one-half as great in the former as in the latter. In no case of previous prolapse or procidentia did cancer occur in the retained stump. He is also of the opinion that unless the mortality from total hysterectomy can be shown to be the same as or less than that for supravaginal hysterectomy, the possibility of later cancer of the cervix should not be considered as an indication for complete extirpation.

As a result of their study of 38 cases of stump cancer examined at the Manchester Radium Institute, Nuttall and Todd⁹ classify these cases into 2 groups: Group A consists of coincident carcinoma which was present at the time of hysterectomy or discovered within such time as to justify the assumption that the growth was then present. Group B includes the true stump cancers which were discovered 2 or more years after the hysterectomy. The prognosis varies with the groups. In Group B it is relatively good, being at least the equivalent of that of ordinary cancer of the cervix. In the first group it is very bad. The generally accepted view that the prognosis is poor arises from the consideration of the 2 groups as a single entity. The good results obtained in true stump cancer do not support the contention that subtotal hysterectomy should be abandoned because of the risk of subsequent malignant change in the stump. The bad results obtained in coincident carcinoma are analogous to those obtained following any incomplete operation elsewhere in the presence of malignancy. They are the result of missed diagnosis and emphasize the importance of careful pre-operative examination.

In the series of over 500 cases of supravaginal hysterectomy which

Scheffey¹⁴ reports, the incidence of the later development of cancer of the cervical stump is calculated as 0.902%. He stresses the importance of pre-operative treatment of the cervix and shows that of 170 patients who had such treatment only 1 developed stump cancer, an incidence of 0.508%. On the other hand, of 384 patients who received no cervical treatment prior to supravaginal hysterectomy, stump cancer developed in 4, an incidence of 1.04%, or twice that which occurred in the other group. When stump cancer develops, it should be treated by irradiation, using both radium and Roentgen ray. He reports a series of 10 cases, 4 treated with radium alone, 5 with radium and Roentgen ray and 1 with Roentgen ray alone. Three of these are alive and well 8 years after treatment, representing a 5-year salvage of 42%. One is alive and well 4 years after treatment and 1 is alive and well after 2 years. Considering the entire group, this represents a present-day salvage of 50%, which is certainly a very creditable report.

Healy and Arneson,⁴ in discussing a series of 67 cases of stump cancer seen at the Memorial Hospital, New York, also agree with the previous authors that the low incidence of stump cancer does not justify routine total hysterectomy. These cases have been treated by irradiation with a 5-year salvage of 14%.

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REFERENCES

- (1.) Burford, T. H., and Diddle, A. W.: *Surg., Gynec. and Obst.*, 62, 701, 1936
 (2.) Ernst, S.: *Zentralbl. f. Gynak.*, 58, 485, 1934 (3.) Goodall, J. R.: *Am. J. Obst. and Gynec.*, 32, 628, 1936 (4.) Healy, W. P., and Arneson, A. N.: *Ibid.*, 29, 370, 1935 (5.) Heaney, N. S.: *Ibid.*, 30, 269, 1935 (6.) Kretzschmar, N. R., and Gardiner, S.: *Ibid.*, 29, 168, 1935 (7.) Marx, R., Catchpole, H. R., and McKennon, B. J.: *Surg., Gynec. and Obst.*, 63, 170, 1936 (8.) Meigs, J. V.: *Am. J. Obst. and Gynec.*, 31, 358, 1936 (9.) Nuttall, J. R., and Todd, T. F.: *J. Obst. and Gynec., Brit. Emp.*, 42, 860, 1935 (10.) Pearse, R. L.: *Surg., Gynec. and Obst.*, 58, 845, 1934 (11.) Read, C. D., and Bell, A. C.: *J. Obst. and Gynec., Brit. Emp.*, 40, 749, 1933. (12.) Richardson, E. H.: (a) *Am. J. Obst. and Gynec.*, 30, 237, 1935, (b) *Ibid.*, 32, 641, 1936 (13.) Rubin, I. C.: *Ibid.*, 33, 137, 1937 (14.) Scheffey, L. C.: *J. Am. Med. Assn.*, 107, 837, 1936 (15.) Siddall, R. S., and Mack, H. C.: *Surg., Gynec. and Obst.*, 60, 102, 1935 (16.) Tamis, A. B.: *Am. J. Obst. and Gynec.*, 28, 48, 1934.

DERMATOLOGY AND SYPHILOLOGY

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PUBLIC HEALTH PROBLEMS: METHODS AND POLICY IN THE CONTROL OF SYPHILIS.

THE control of venereal ("genito-infectious"^{24c 27b c e}) disease, and of syphilis especially, has long had passive recognition at the hands of public health authorities as one of the major disease problems of the

world. Within the past decade a wave of interest has been gathering headway and has been brought to a crest with the appointment as Surgeon-General of the United States Public Health Service of Dr. Thomas Parran, Jr. It is Dr. Parran's evident intention to give to the problem of syphilis during the next decade or longer a very substantial share of the energies devoted to public health in this country. An orientation with respect to the problem and its bearings on medical practice is, therefore, timely and important.

The foundation for any program of such importance is an adequate study of prevalence, and this the United States Public Health Service has been developing in this field, with the coöperation of other agencies such as the American Social Hygiene Association. The most authoritative recent review of this work is that presented by Dr. R. A. Vonderlehr,^{47b} in charge of the Division of Venereal Diseases, U.S.P.H.S., at the December Conference on Venereal Disease Control, Washington, December 28-30, 1936. On the basis of one-day cross sections and other statistical determinations, it is now definitely known that the minimum number of persons in the United States constantly in need of medical care because of syphilis is 683,000, or 4 per 1000 population.⁴⁵ Annually in the United States one-half million cases of early syphilis seek authorized medical care.^{47b} There is a large though undetermined number of individuals acquiring the infection who neglect treatment until some late manifestation forces them to have attention. As Vonderlehr points out, the disease is never thought of as epidemic in the United States, yet annually there are twice as many new cases of syphilis as scarlet fever, 13 times as many as diphtheria, 28 times as many as typhoid, and $1\frac{1}{2}$ times as many as of tuberculosis. The attack rate for syphilis based on a New York State survey is $2\frac{1}{2}$ times as great in cities over 10,000 as in cities under 10,000, being 41.6 per 100,000 in the larger cities. The urban attack rate was 40% higher than that for upstate New York. Incomplete reports substantiate the statement that the incidence of the disease is highest in the South, owing to the presence of a large infected negro population. Analyses of the age, sex and marital status bring out conspicuously the youthfulness of those infected. It is estimated that 100,000 acquire the disease before 20, and even that 11,000 acquire it between the ages of 11 and 15. The incidence of syphilis in the colored race is twice that in the white, and twice as high in the single male as in the single female.^{27f}

The trend of the disease in this country has been investigated as a significant guide to what will be required in its control. From 1919 to 1930 there has, of course, been a gradual increase in the rate of reported cases for the country as a whole.^{46a} Special surveys have been made to avoid the obvious error of statistics based on mere increase in reported cases. From such one-day censuses in special communities aggregating $8\frac{1}{2}$ million in population, it is apparent that the prevalence rate of syphilis increased between 1927 and 1933, 3.4%. Between 1930 and 1934 in Massachusetts, it increased 1.5%, the rate for the female increasing 12 times that for the male.^{27f} The morbidity surveys of upstate New York have shown an increase in the prevalence rate for all stages of syphilis of 32%.^{47b}

In contrast to this general increase, surveys of special localities for early syphilis have shown such figures as a decrease of 13% between

1927 and 1933 in 17 selected communities,⁴⁵ a decrease of 31 % between 1927 and 1935 in Massachusetts;²⁷ and of 45 % in upstate New York during the same period. This decline in early syphilis, as will be seen, is accepted throughout the world as one of the most usable and hopeful criteria of public health control for the infection. Late syphilis increased in the respective groups above mentioned 11 %, 19 % and 60 %. Syphilis in pregnant women, on the other hand, offers a hopeful contrast with a striking decline in certain special areas such, for example, as the State of Massachusetts, in which Hinton's examination²⁷ of the serologic reactions of nearly 8000 pregnant women between 1915 and 1919 and 17,000 pregnant women between 1930 and 1934 indicated a reduction of 70 % in positive and 76 % in doubtful serologic reactions in spite of the recent employment of much more sensitive tests for a 9 months' period in 1934. A review of stillbirths, in which syphilis is reported as the etiologic factor shows no decline between 1922 and 1933, but there is a decline in the general mortality of infants due to syphilis from 0.86 to 0.52 between 1921 and 1933.⁴⁴

Cardiovascular syphilis, so far as available figures indicate, is showing a downward trend in spite of the upward trend of heart disease at adult ages in the general population. In 1914, at the Massachusetts General Hospital, 12 % of a group of cardiac cases were due primarily to syphilis, while in 1928 the proportion due primarily or secondarily to syphilis was 5 %.⁵⁰ A reduction of 20 % has occurred in aneurysms in the same hospital,⁵ and aortic insufficiency and aneurysm have dropped 40 % in the United States Army in the 10 years ending 1934.

In the field of neurosyphilis, first admission rates for paresis in 500 institutions in the United States show no change from 1922 to 1933, while first admissions for other causes than paresis have increased 17 %. In Massachusetts, a slow decline has been apparent for males since 1920. Mortality data for paresis in the registration area of 1900 indicated a decline from 1916 to 1933. In New York and Massachusetts, there has been a rapid decline from 1924 to 1927, but since 1928 the rate has remained stationary at 3.8 per 100,000 population. The death rate for *tuberculous dorsalis* declined from 3.0 in 1915 to 0.9 in 1933.^{46b}

It is apparent then, that syphilis is a major, if not *the* major national health problem, that the disease itself is at least not on the decline in this country, though the incidence of early syphilis where public health measures are achieving some degree of success is definitely decreasing.

The Medical Situation. Controllability of Infectiousness and Prevention of Late Complications. A number of summaries of today's medical situation with respect to the disease, and particularly to that of control by prevention of infectiousness are available.^{6,9,16,24b,29,40,41,47a} The inspiration to much of the work that has clarified and organized our conceptions on this matter should be traced to the Health Organization of the League of Nations, which in 1928 organized the Commission of Experts on Syphilis and Cognate Subjects which, under the chairmanship of Jadassohn, drew up a comprehensive scheme for international study of therapeutic methods and results in the early phase of the disease. From this, in its various national ramifications, sprang the inspiration for the Coöperative Clinical Group and the United States Public Health Service studies of American methods and results which today form the most tangible and dependable basis for American

practice side by side with their incorporation into the International Treatment Standard formulations of the League of Nations Commission. A convenient summary of the principles involved in the use of treatment for the control of syphilis is that of Moore (Chairman's Report in Proceedings of the Conference for Venereal Disease Control Work, Washington, D. C., December 28-30, 1936).^{24a} As an indication of the source to which public health must turn for help in the treatment of the disease, it appears that 55 % of the physicians engaged in private practice in this country do not treat syphilis at all. Slightly more than 50 % of all patients known to have the disease are treated in clinics. Clinic treatment is in general better in quality than that given in private practice. In practically all communities in the country the demand on private practitioners for treatment should be increasing, but in spite of this, almost everywhere the facilities now available are unquestionably inadequate to meet the potential case load. Clinic practice in this country is at present estimated to be only 25 % efficient, and for the potential case load only 10 % efficient. It is felt, therefore, that the clinic rather than the private practitioner is the backbone of the community program for the control of syphilis. There need, however, be no conflict between clinic and private practice for there is easily enough for both. The major emphasis of clinic practice should be on the treatment of the patient with infectious early syphilis. Where the syphilis clinic is not part of a general hospital, expert consultation service should be developed, a need, indeed, which is felt throughout the entire field of public health and private management of the disease at the present day.

The amount and kind of treatment required to control syphilis as an infectious disease has been reviewed in the publications of the Coöperative Clinical Group^{10a, b, 24c, 28, 43a} and is summarized by Stokes⁴⁰ and by Moore.^{24a} Quoting Moore, the principles involved in the management of early syphilis presuppose that the average patient is a healthy young adult free from complicating diseases. The manifestations of syphilis are uniform in this type of patient and uniform results are achieved with a surprising regularity under standardized modes of procedure. The broad principles established by the Coöperative Clinical Group and United States Public Health Service studies and in the work of the League of Nations Commission of Experts are as follows: Results of treatment by two systems, the Danish-British Intermittent System and the American Continuous type of treatment are authoritatively established. For American practice the Continuous System is the more acceptable standard and presupposes in the management of the early infection no rest period of any kind until arsenical treatment is finished. Treatment must be prolonged for a minimum of 15 to 18 months regardless of serologic findings at the time the disease is diagnosed and regardless of serologic progress during the treatment. For the control of infectiousness a minimum of 20 injections each of an arsphenamine and a heavy metal (preferably bismuth) are essential. For the accomplishment of individual cure a minimum of 30 injections of an arsphenamine and 40 of a heavy metal are desirable. Lifelong post-treatment observation with periodic reëxamination has the support of many observers, but modifications of this requirement have

been suggested by the study of the question made by Stokes and Usilton.⁴¹

The system of treatment carrying out these principles which has been laid down by the United States Public Health Service as the basis of effective practice for this country is what is technically spoken of as the Continuous-Alternating technique. That is, the arsenical drug is given for a series ranging in the case of old arsphenamine (606) from 4 to 6 injections, and of neoarsphenamine (914) from 8 to 10 injections at weekly intervals, the first 2 or 3 injections being perhaps crowded into the first 10 to 15 days. Upon the completion of this arsphenamine course, or commencing simultaneously with the last injection or 2, the patient receives bismuth salicylate intramuscularly for a series of injections ranging from 4 to 6 at weekly intervals. The patient then resumes his arsenical for a second course, approximating in length the first course and again at its close receives bismuth exclusively for a period similar in length to that of the first bismuth course. Thus, courses of arsenical and bismuth alternate with or without overlapping until the patient has received the optimum of 30 injections, or more if any indications for prolongation of treatment have arisen (*e. g.*, fluctuating or weak positive serologic tests, symptomatic recurrence, and so forth). Following the completion of the arsenical and bismuth alternating phase of the treatment, the patient continues bismuth intramuscularly and for the first time in his course is allowed brief rest periods of 4 to 6 weeks between bismuth courses of 6 to 10 injections. When the patient has received a total of at least 30 arsenical injections and from 40 to 60 bismuth injections he is rated as ready for 2 years' probationary observation provided his course up to this point has been absolutely uneventful. An essential feature in the management of every case of early syphilis is the examination of the spinal fluid, which should be properly performed between the sixth and twelfth months of treatment and certainly before the first rest period is granted. It should be made clear to American practitioners that the continuous-alternating system just described is unquestionably superior to any of the American forms of intermittent treatment. Repeated studies^{39b, 40, 43a} have demonstrated very clearly that the lapse, or rest period is in American practice responsible for drops in ultimate efficiency ("cures") ranging from 10 to 40%. The absolute curative efficiency of continuous-alternating treatment at the most favorable period of the disease, namely, the seronegative primary, is 86.4%. It seems probable in resurveys now in process that the absolute efficiency of this system of treatment will ultimately range in the 90's. Curiously enough it appears that the use of the continuous-alternating system of treatment in fully developed secondary syphilis yields better results than would ordinarily be expected; namely, 81.5%.

The influence of continuous-alternating treatment upon the incidence of infectious relapse has been repeatedly reviewed^{40, 42, 43b} and need not be dealt with here beyond the statement that the continuous-alternating system above described has, in all particulars connected with relapse, an unmistakably higher efficiency rating than that of American types of intermittent and irregular treatment.

It is an aphorism to be dinned into the ears of the medical profession

by every possible device that late syphilis is the consequence of inadequately managed early syphilis. To this statement also the observations of the Coöperative Clinical Group have given statistical background. Cardiovascular syphilis,^{100, 396} for example, developed in 1.6 % of 935 early syphilis patients followed from 3 to 10 years and in 6.7 % of 105 patients observed from 10 to 20 years; but not one who had had adequate treatment for early syphilis developed a serious cardiovascular lesion in the 3- to 20-year group. A Coöperative Clinical Group survey of asymptomatic neurosyphilis, with O'Leary as spokesman,²⁸ demonstrates that adequate treatment given by the Continuous System results in the lowest incidence of neurosyphilis (11.7%) of any form of treatment now available. The ancient bugaboo of supposed predisposition to neurosyphilis by modern treatment methods has by this study as well as a number of others been embalmed for decent burial.

In no aspect of the transmission of syphilis has its controllability by adequate treatment been more fascinatingly or effectively demonstrated than in the field of congenital infection of the fetus. The treatment of the pregnant woman has revolutionized the situation for the child. The pioneer work of Boas and Gammeltoft³ has found effective continuation in the demonstrations by McCord,²² Bartholomew² and others in the United States of the striking protective value of treatment of the mother for the potentially syphilitic child. The principles, as understood today, are summarizable in terms of the time in the pregnancy when treatment is begun and the amount of treatment administered. The serologic state of the mother during the pregnancy also influences the outcome; a mother seronegative during pregnancy has an 81 % prospect of a healthy child, while a mother seropositive during the pregnancy has only a 57 % prospect of a healthy child.^{10a, 396} If treatment is begun before the fifth month the prospect of a healthy child aggregates 78 % as compared with 61 % if treatment is begun after the fifth month. If 10 arsenical injections and 10 heavy metal injections are given before the fifth month, 91 % of the children are healthy. The preponderance of arsphenamine over heavy metal in the treatment scheme favors the birth of a healthy child. With reasonable attention to the established rules for the prevention of complications, the pregnant woman is an admirable subject for treatment and, in fact, tolerates it somewhat better than the non-pregnant woman. Regardless of serologic status there can be no question that the untreated syphilitic woman is a potential carrier of infection for the fetus up to 10 or 11 years after she acquires the disease. In fact, the untreated seronegative pregnant woman in the CCG statistics gave birth to only 28 % healthy children.

It is apparent then, that treatment is the strong right arm of practically every aspect of the control of the disease today. To find the infected individual, to find him early, to treat him continuously by a combined arsenical and heavy metal therapy to an already established optimum standard is the essence of the matter.

The Control Setup With Its Possibilities and Limitations. To all students of the problem it is now apparent that if an arsphenamine can be brought to each infected individual in adequate amounts with regularity, our mastery of the disease can be all but complete. For the demonstration of this fact we are indebted not alone to the clinical observations of disappearance of *Spirochæta pallida* from infectious

lesions within 24 to 96 hours following a single injection, but to what might be regarded as public health laboratory experiments in the control of syphilis, of which the technique of the Scandinavian countries during the past half century has been the outstanding model and "health demonstration." The principles established by the Scandinavian type of organized attack on the disease have been admirably reviewed by the New York Commission, appointed to study various phases of continental experience.⁸ It is important to understand both the application and limitations of the Scandinavian procedure, because they are now so widely used as an argument for the infallibility, one might say, of public health control of the disease. The Danish scheme in operation in many of its essentials since 1788, provides first, for the reporting of all cases of syphilis and gonorrhea, but not by name unless delinquent; free treatment (July, 1790); compulsory treatment (1874); legal prohibition of prostitution and solicitation (1906); and the assumption by the State of the entire cost of providing for the diagnosis and treatment of all cases of syphilis and gonorrhea (1932). Here, then, clearly outlined, is the skeleton framework upon which, as a public health issue, the control of syphilis must be built.

Some notion of the effectiveness of the Scandinavian program for the control of syphilis may be gained statistically from the incidence rates for the disease in three representative cities; in 1919 as compared with 1934. In the city of Copenhagen the rate fell from 527 to 28 per 100,000. In Stockholm, the rate declined from 450 to 7 per 100,000. In Oslo, the decline was from 350 to 30 per 100,000. Such figures as these which foreshadow a virtual extinction of the disease in the communities concerned constitute the basis for the prevailing optimistic statement in national antivenereal programs throughout the world.

It is important for the student of these questions, however, to realize that such results as these when examined from other angles are susceptible of varying explanations not necessarily associated with the effectiveness of a public health campaign. Moreover, it must be realized that in the Scandinavian countries highly special conditions prevail which can be reduplicated only with the greatest difficulty, if at all, through a large part of even the civilized world. A homogeneous population long accustomed to public health practice and with a medical profession thoroughly imbued with the disciplined conception and thoroughly equipped with the high standard of educational and practical accomplishment necessary for such a task inevitably constitutes a unique rather than a general demonstration of the possibilities before us. That it is possible, however, by even less ideal applications of the principles above set forth to bring about substantial reductions in the incidence of venereal disease, has been illustrated for our own state of Massachusetts which in many particulars reduplicates the special characteristics of the Scandinavian countries. In intelligence and intensiveness the movement against syphilis under Nelson's direction in this State achieves a high for American accomplishment today. Nelson²⁷ finds that neurosyphilis in Massachusetts has sustained in 4 years an incidence reduction of 32.3%. This is confirmed in several directions. Syphilis in pregnant women in 15 years has been reduced 70%; admissions to syphilis clinics in 10 years in spite of an expanding program have been reduced 30%. The latest available statistical data from

New York State, whose program ranks with that of Massachusetts in effectiveness, very closely parallels the Massachusetts trend.^{46a}

Whether the optimism engendered by these successful local programs can be justified in a national field is, of course, an important question for which the evidence in Great Britain is quite widely accepted as valid.

As a nationwide setup for the control of venereal disease, that of Great Britain has many features applicable to practice conditions in other larger countries, including the United States, and these should be summarized in order to add point to the figures indicative of the degree of their success.⁸ The public health services of Great Britain are combined under a single central governmental agency, the Ministry of Health. The actual provision of facilities for control of the venereal disease situation is, however, local, through the County Councils and County-Borough Councils which, of course, recognizes the extremely important local phase of the control of this type of disease. The influence of the Ministry of Health, however, exerted through Colonel L. W. Harrison and conditioned by its larger share in the finance, is paramount. It has made possible the development of uniform high-grade free diagnostic laboratory service confined to approved laboratories throughout the United Kingdom, and control of placement and operation of clinics comparable to that possible in municipalities and smaller countries like the Scandinavian. The free distribution of drugs has served to indicate the partition of the existing treatable syphilis between private practitioners and public clinic agencies, and shows that only about one-sixth of all treatment conducted is carried on outside of government clinics. The profession at large may therefore be judged in Great Britain, practically to have surrendered the venereal disease problem except in a few of its special aspects, to the State. Three-fourths of the cost of treating venereal disease is borne by the central government which naturally makes the local authorities amenable in the highest degree to suggestion and coördinative advice. Something short of \$2,500,000 is the approximate annual expenditure involved, which affords a species of measuring tape for what should be expected in larger countries like the United States.^{12, 27d} This is interpreted by Colonel Harrison as approximating 5 cents per capita per annum. It is a striking fact in British venereal disease practice that the reporting of venereal disease whether by name or number to central authorities and the use of any form of compulsion in the acceptance and continuance of treatment has thus far been avoided. The improvement in the control situation in Great Britain may, therefore, be interpreted as a product of education rather than force.

The number of cases of syphilis dealt with for the first time in treatment centers throughout England and Wales has been reduced from the peak of 1920, 42,805 cases, to 19,335 in 1935. This represents a 55% reduction and indicates that the volume of syphilis has declined within 15 years, since the peak, to 45% of the original figure. Cases of syphilis with infections of less than a year's duration have been reduced from an incidence rate of 2.28 per 10,000 population to 1.47 per 10,000 population in the 5-year period 1931-35. This is a reduction of 35%. The death rate from infantile congenital syphilis has been reduced 86% from the peak year in 1917 to the low of 1935.¹

The Obstacles to Syphilis Control. The optimism inspired by the apparent logic of the situation, particularly as regards the chemotherapeutic control of infectiousness and the statistical evidence just cited from various sources, cannot be accepted without critical analysis. This was attempted by Stokes^{39b} in a consideration of the obverse side of the picture. Pointing out a number of as yet unanswered problems concerning the *Spirochaeta pallida* itself and the reservoir of infection in the asymptomatic carrier together with such considerations involving the granular form of the organism and possible relations to virus diseases, this author calls attention to the inconveniences and difficulties of 'dark-field' diagnosis, which will probably require the development of a centralized mechanism, and the margins of uncertainty and error involved in serologic tests especially from the standpoint of their technical performance. He points out that the anti-syphilis campaign from the standpoint of publicity and promises is proceeding far ahead of a rational expectancy for the development of adequate facilities. For example, the proposal to have a serologic test for syphilis become part of the examination of 7,700,000 annual admissions to medical and surgical beds as the first step in uncovering the infection in the population at large, is in itself an undertaking for which no large nation and certainly not the United States, is anything like prepared (cf. Moore^{24d}). When, in addition, the total of out-patient and dispensary examinations is included; when it is estimated that 3,000,000 new syphilis patients annually will be uncovered, 650,000 of them fresh infections, it is apparent that the money and generalship alone required for this single phase of the enterprise will be very large. The lethargy of the physician where such routinization is involved, the attitude of the courts,^{39b} and most recently, the inadequacies of the performances of laboratories themselves,¹¹ all gravely influence the future of this most important detective effort. While there has been a substantial increase in alertness, the great primary essential to the recognition of syphilis and the comprehension of its behavior in any and all phases, there is no question that the teaching of medical students and the knowledge of the general practitioner at the present time, both in diagnosis and in treatment are wholly inadequate to the responsibilities involved in the new campaign. The *terra incognita* of the woman's genital tract, the bearer of the large proportion of infectious lesions during the critical transmissible period is emphasized. Epidemiology with respect to syphilis is still in its infancy. There does not exist at the present time even the necessary trained personnel to undertake the difficult and exacting detective work of tracing the devious course of syphilis through the community. That such a personnel can be developed is a foregone conclusion, but the time involved will certainly not bring the control of syphilis and its extinction as a disease into the 30 years of an ordinary generation. The influence of money, vice and alcohol has by no means diminished in recent years, and much must be learned and relearned from studies of this problem whose titles are now all but forgotten in the literature. Female passive transmission of the infection; the extent and possible extension of perversion also bids fair to take its part in the final reckoning.

The treatment control situation contains intrinsic difficulties of which

enthusiasts often lose sight. The minimum treatment adequate to the control of infectiousness constitutes in reality not the magic wave of a wand as so often depicted, but a tedious, exacting, inconvenient, costly, sometimes dangerous procedure, demanding of the patient a more than average display of character, and of those who care for him an extraordinary knowledge and tact in dealing with human nature. Granted even that patients, actual and potential, can be educated to the point of maximum coöperation, there still lies before the venereal disease control movement a vista of educational effort directed at the medical profession itself for which present-day provision is wholly inadequate. Wile⁵¹ has pointed out that 58 of 63 undergraduate medical schools surveyed in the United States make only the most skeleton and inadequate provision for instruction in syphilology, and Stokes and his co-workers at the University of Pennsylvania Clinic³³ have pointed out clearly how even minor technical slips in treatment given by supposedly skilled organizations act to break up the allegiance to treatment and the ability to continue it which is so vital a part of the present-day program. Prophylaxis, mechanical and chemical, has critical weaknesses inseparable from human nature itself which are too seldom considered by enthusiasts and which can be dealt with only by a fundamental reëducational program of the most comprehensive sort. The decline in the incidence of syphilis, while demonstrated by the figures previously cited, has flies in its ointment, too. It is by no means general throughout the world, and the existence of waves in the epidemiologic curve of syphilis have been pointed out by von Düring⁴⁹ and Gumpert,¹⁵ and suggested by Källmark's²⁰ mathematical analysis. In spite of widespread educational effort, treatment for syphilis must be rated as substandard throughout the larger part of the world, and this has been already responsible for bringing to a standstill programs and prospects such as the Belgian, which seemed at the outset certain of success (Schwers³⁶). The adverse influence of travel, of fluid population, of heterogeneity in language and race, and of the limited effectiveness over a period of years of publicizing educational method must all be rated as obstacles to be met and overcome. Modern sex life is for the moment frankly against the movement for the control of venereal disease. Fear itself, long an actual, though sometimes over-rated deterrent, is rapidly losing what influence it has had. Even the clinic, rated as the most powerful instrument in carrying through treatment prevention, has been repeatedly placed in a thoroughly unfavorable light. The international investigation by the League of Nations Commission of Experts disclosed inadequacies in diagnosis and treatment among the selected clinics of the world which were a shock from an unexpected source. The methods for separating the 18 to 20 % of onsets of syphilis from their gonorrheal masks are still imperfect, not so much in themselves as in the practically total failure to apply serologic follow-up and adequate personal examination to the patient with the less distinguished venereal disease.⁷ McKneely's²³ recent study of venereal disease clinics in this country is a devastating indictment, which should be read, and pondered and acted upon by the head and personnel of every venereal disease clinic in the world.

The American Program. It must be apparent then, that despite the intrinsically favorable situation, only the finest and most deter-

mined planning and action can make reality out of the enthusiastic hopes of many of the most distinguished personalities in this field. The American program, though heralded by a sudden puff of press enthusiasm and support as expansive as it was unexpected, is endeavoring to keep its feet on the ground and to proceed step by step to utilize the advantages and meet the difficulties above described.

Four factors promise to be of primary importance in the movement. The first of these, historically speaking, is the work of the Coöperative Clinical Group, stimulated by the International, or League of Nations Investigation, and carried forward in detailed studies with the aid of the United States Public Health Service statistical organization far beyond any other study of national scope. This work sets standards of practice never before available to the profession. In the 5 University Clinics of the Group* plus those of several collaborating agencies, a total material of approximately 75,000 cases has been gathered. Reports covering early syphilis^{24a,b, 40, 41, 43a} (6807 cases), latent syphilis^{24c} (1936 cases), syphilis in pregnancy^{10a} (3817 cases), late prenatal syphilis^{10c} (1010 cases), cardiovascular syphilis^{10b} (10,614 cases), and preliminary studies of neurosyphilis²⁸ (5293 cases), are already in print, the collected papers constituting a massive large scale textbook of modern procedure in the diagnosis and treatment of the disease from the standpoint of American practice. Physicians whose interest has been stimulated by the public health authorities, and the general publicity attitudes towards the disease would be well advised to secure through the United States Public Health Service reprinted material from these studies as the most recent and authoritative statement of therapeutic ideals easily available to them. Under a permanent form of organization the Coöperative Clinical Group is continuing the effort to interpret into practical and usable terms the modern treatment of the disease including through the work of subcommittees the relative values of various methods of fever therapy and so forth.

The second influence which has unquestionably given the venereal disease control movement the prestige it has so long lacked is the outspoken expressions and policy of the Surgeon General of the United States Public Health Service, Dr. Thomas Parran, Jr. Challenged at the start by the refusal of one of the national broadcasting companies to permit him to discuss the subject of syphilis over the air, his persistent efforts^{30a,c,d} in the matter have enlisted the interest and coöperation of even the most lethargic members of the profession, the press and the public.

The third potent influence for the successful future of the syphilis control program is the provision of the sinews of war in the form of funds under the terms of the Social Security Act, allocated to the United States Public Health Service, and by them distributed on a dollar for dollar basis to the state health authorities of the country. No such provision has been available since the war emergency legislation of 1917.

A general outline of the American program can be obtained from the report of the Advisory Committee to the Surgeon-General, published by the United States Public Health Service in January, 1936.⁴⁸ This program provides that the State, municipality or health district which plans to open a campaign against venereal diseases should inte-

* Syphilis clinics of the Mayo Clinic, Western Reserve University, Johns Hopkins University, University of Pennsylvania, and University of Michigan.

grate this work with the communicable disease division of its health department, but give it the separate direction and high individual autonomy implied by a full-time venereal disease control officer. A local advisory committee to the Health Department, coördinating the interests of the venereal disease division, the medical and allied professions and all voluntary agencies, is to be established in each of these jurisdictions. An adequately organized program and proportionate assistance determined by the State's venereal disease morbidity rate are provided for. Adequate treatment facilities in urban communities are to provide (1) for the diagnosis and emergency treatment of any patient who applies, or (2) of any patient who is referred by a private physician either for continued treatment or for consultative advice and opinion; and (3) finally, for any patient who is unable to afford private medical care. The establishment of clinic facilities is to be made a matter of conference among the various instrumentalities concerned, including medical school, local hospital, research and philanthropic societies with the local organized medical profession and the state and national Public Health Service. Polyclinics are preferred to isolated clinics and the support of subsidized hospitals and health centers is made contingent on their coöperation in the state program. The admission of patients to beds when required for the treatment of syphilis and gonorrhea is made a condition of continued support. Provision is made for the development of a record system for transients and transferred patients; in communities with inadequate treatment facilities surveys are provided for, followed by a conference of all concerned and a full discussion of the questions of enlisting the coöperation of local practitioners, organizing branch clinics, new clinics, publicity and so forth. The need for abolition of quack remedies and drugstore prescribing is emphasized. In rural communities, emphasis is laid on the subventionary assistance of properly qualified local physicians, the services of specially trained county health officers, special provision for transportation of patients to centers, and the development of large special treatment centers in areas such as the deep South where many negro patients are concentrated. Traveling health units are also suggested. It is stated that the free distribution of antisypilitic drugs by the State to all sources of treatment is rational and proper, and it is advised that two arsenicals and one bismuth preparation be the minimum made available in such a program. The development of a venereal disease diagnostic and treatment center of high rank in each state is strongly urged to serve as a consultation agency for patients, the profession, and clinic throughout the State. It is impossible here to go into details of planning and organization of clinics which must be read by interested persons in the original. The follow-up and contact-tracing personnel is specified as requiring special training and full-time service.

The standard treatment systems outlined by the Coöperative Clinical Group are recommended as standard for municipal, state and national procedure insofar as the subject is thus far covered. Serologic testing of every pregnant woman is specifically urged early in the course of her pregnancy as the first rational step in the control of prenatal syphilis.^{30b, 39c}

For the first time in its history the venereal disease control movement gives full cognizance to the great importance of epidemiologic work in

the control of the disease. First sharply pointed by some pungent remarks of Munson,²⁶ this aspect of syphilologic work developed rapidly under the pioneer observations of Dudley Smith and W. A. Brumfield at the University of Virginia.^{4, 37, 38} These authors have shown with a vividness hardly surpassed by any aspect of syphilis control work in recent years both the process by which syphilis disseminates itself throughout a community and the type of detective work which is necessary in ferreting it out and bringing it under treatment control. Coincidentally, follow-up, long a species of stepchild in the majority of syphilis clinics, has received new and more serious recognition.^{13, 18, 21, 25, 27a, 33, 35} Both these fields are now conceded to require careful special training for those who devote themselves to them.⁴⁸

In the matter of laboratory facilities, the Advisory Committee has unhesitatingly urged the standardization by the State of all sero-diagnostic procedure, with the maintenance of a careful check even to the point of licensing of private laboratories performing this work. Studies of a large number of laboratories throughout the country conducted as the so-called First Serologic Conference by the United States Public Health Service, have shown astonishing discrepancies in the work of various laboratories within a State, and the various State laboratories themselves.^{11, 32} It is very apparent that this subject must early engage the full attention of central and state agencies if anything like the necessary reliability and availability of our most important uncovering device, the blood test, is to be utilized. The practice of Great Britain which exercises a systematic central control of all its official stations throughout the British Isles can provide something of a model for practice in this country. The recommendations³¹ of the Committee on Evaluation of Sero-diagnostic Tests for Syphilis, headed by the Surgeon General of the United States Public Health Service, begins with insistence that adequate training is necessary for all employees and that Social Security Act funds may be appropriated to bring the personnel up to an adequate standard. A system of periodic inspection of State laboratories by thoroughly trained serologists with the United States Public Health Service is to be inaugurated and made available at the request of state health officers, and comparative examinations of serologic test performance in syphilis are to be made annually. The venereal disease research laboratory of the United States Public Health Service at Stapleton, Staten Island, New York, is drawn into this work. Municipal, private and hospital laboratories are to have a comparative annual examination through the action and support of the State Laboratory organization. In return for this cooperation it is recommended that local laboratory facilities and properly qualified and subsidized local laboratories be utilized to the full in the control of syphilis.

Among the specific items on serologic test performance it is recommended that standards for the handling and drawing of blood specimens be promulgated by the Public Health Service;⁴⁸ that the technique of the originators of tests should be strictly followed by all laboratories and modifications allowed only with the approval of the central state laboratories; that laboratories be required to use the terms "positive," "negative," and "indeterminate-repeat" (doubtful) in reporting the results of sero-diagnostic tests; and that it should be made clear that

while a single test may be used by a laboratory as a first line diagnostic procedure, the adequate serologic investigation of a doubtful or indeterminate result requires not only repetition of the original test but also the simultaneous use of another test of a different type. In the field of darkfield examination, States are advised to establish laboratory coöperation for direct darkfield examination and to provide mailing kits for practitioners, with suitable publicity relative to their availability and use for the indirect darkfield examination. The examination of the spinal fluid performed at some time during the second 6 months of treatment in early syphilis and as near the start as possible in late syphilis is made a standard procedure.

The anxiety which besets some physicians lest venereal disease control be removed from the field of private practice and taken over completely by the State should be to some extent relieved by the positive assertions of policy with reference to the coöperation of private physicians. The State function is specifically outlined as consisting of (a) the provision of free diagnostic service of high grade, (b) the free distribution of antisypilitic drugs to private physicians for use in the treatment of private patients who are or may become a danger to public health, and (c) the provision of consultation services, including roentgenologic and other expensive laboratory examinations for indigent patients or those normally unable to pay for expensive service. The State health organization is expected to provide the physician with modern information on the control of the disease and to encourage him in every way to prepare himself to meet the public's and the health authority's demand for an adequate standard of treatment.

In the matter of morbidity and mortality reports, the American program provides for the reporting of all cases by a numerical system including the place of residence, but not the name of the patient (*cf.* Ramsey³⁴). Laboratory reports are not to be accepted as case reports. An exceedingly important feature of the modern venereal disease program is the informative and educational program for physicians. There can be no escaping the conviction after a study of this problem that the most serious difficulty confronted by a venereal disease program in a country such as the United States, where a large proportion of patients with gonorrhea or syphilis receive treatment at the hands of private physicians is that of raising the physicians' standard of knowledge and technique to that of the modern clinic, or above it. Reference has already been made to the inadequate teaching of medical students in syphilology and ways and means of improving it are considered by the Advisory Committee.⁵¹

In a discussion of these problems by Stokes,^{39c,d} it was suggested that energy be concentrated on the physician as early in his career as possible; that in view of the demonstrable inadequacies of simon-pure oral and written didactic methods, an effort be made to concentrate on the visual, on the individual case example, and on the actual performance of technical procedure and the giving of instruction upon the patient in small groups.

Incorporation of more searching questions regarding venereal disease practice in the State Licensing Board examinations is advocated in the Public Health Department recommendations. Physicians having a special interest in venereal disease problems from their hospital intern-

ship onward, are to be made objects of special interest and solicitude by the health authorities; and on letting their interest be known they will be given every possible encouragement to learn the field and work in it. Subsidies to medical schools and teaching hospitals are recommended and a system of postgraduate instruction for practicing physicians, utilizing state, federal and academic instructional centers awaits development. Consultative service by telephone, telegraph and correspondence on a regional basis is proposed as part of State service to the practicing physician. The dissemination of informative material, including the monthly journal of the Division of Venereal Diseases of the United States Public Health Service—"Venereal Disease Information"—is emphasized.

In a public health movement of this sort, the possibility of educating the public and thus the potentially infected patient to the point where he may insist upon and, indeed, actually solicit proper antisymphilitic therapy, should engage the thorough study of any civilian public health informative program.^{39a} The "backfire" educational influence on the profession of an informed public, including many societies with collateral interests such as antituberculosis organizations, public health nursing, penologic and child hygiene organizations, health councils, social agencies, parent-teacher and women's clubs is recognized and should be fostered as a means of raising medical treatment standards of practice through the influence of the informed patient. The minimum essential knowledge for the student and physician for meeting these demands could be offered by clinic and teaching hospital organizations as brush-up courses and adapted to the now neglected instruction of interns on a basis of 56 hours of syphilologic instruction, which, under pressure, might even be reduced to 40 for small groups that can be brought into close contact with the patients and equipment. Such courses can easily be given in large cities with teaching and medical centers.^{39c}

In response to the general appreciation among authorities of the great importance of special training for a venereal disease control personnel, it may be stated that a special course has been developed at Johns Hopkins University School of Public Health for the training of public health officers and at the University of Pennsylvania for the training of epidemiologic and follow-up personnel and intensive training of physicians interested in syphilis control work and devoting a portion of their time to this problem.

The fourth influence in the syphilis control campaign is the new publicity especially as reflected in the press. From a condition of affairs in which the very word was never printed, syphilis has become as DeKruif says, a "cozy household word." From the opening of the flood gates by such influential newspapers as the Chicago Tribune, has come literally a torrent of publicity. Whole front page feature articles in Sunday supplements; extended rotograve illustrations of experimental and clinical practice and technique; and the sponsoring by press and health authority of such municipal enterprises as a blood test campaign to cover every citizen of the United States' second largest city, have been expressions of this almost fevered activity. Magazines of national circulation have published the utterances of the Surgeon General, and the technique of treatment of early syphilis has been so published that

he who runs may read. Five popular books are now available where one formerly languished in obscurity. It is difficult to believe that such activity can last. Its value is yet to be determined, but is certainly considerable if not carried *ad nauseam* to self-defeat.

It will thus be seen that the program outlined for the syphilis control movement in the United States embodies practically every essential which theory and previous world practice has indicated as significant. Several lessons have already been learned. The press publicity has already markedly increased the number of persons applying for examination and treatment. Such cities as New York have greatly extended their diagnostic service through the establishment of local stations where examination for darkfield diagnosis especially, can be rapidly and effectively done. It has become very clear that laboratories must be quickly brought up to a very much higher standard of practice than has prevailed heretofore, if there is not to be an enormous crop of falsely diagnosed syphilis to encumber and shed disrepute on the program at large. Studies of the very important problems of contact-tracing and follow-up have indicated that the superiority of the voluntary approach over compulsion or enforcement tactics can be stated in percentage as summarized by the Ingrahams.^{17, 19} This work indicates that the employment of a confidential persuasive approach to elicit a voluntary response from the patient, in the hands of a trained individual, is about half again as productive of usable epidemiological information as is the untrained coercive approach. The voluntary response method is likewise superior to compulsory methods in persuading the average suspected contact to submit to medical examination, and in about the same magnitude.

It is further strongly suggested by a study of persuasive *versus* compulsory methods in four large city clinics, conducted by Norman R. Ingraham, Jr., that voluntary approach is at its highest effectiveness in contact-tracing, but that an element of compulsion is a necessary and valuable part of the procedure of follow-up. Generally speaking, however, the demonstration of the relative superiority of voluntary approach in this field is an interesting confirmation of the point of view long maintained against opposition by the heads of the British venereal disease service.

There seems every probability that large-scale social organization of many types will be drawn in one way or another into the venereal disease control campaign. Conspicuously interesting, therefore, is the report of G. H. Gehrmann,¹⁴ Medical Director of E. I. duPont de Nemours and Company, on the problems which have been encountered on the effort of this great industrial organization to modernize its reactions and methods in the light of present-day knowledge of syphilis. It is notable that no difficulty was encountered in examining new employees, and that less than 10% of old employees refused the blood serologic test for syphilis. In all, 36,794 employees have been examined, and 1488 (4%) found to be infected. The organization operates its own laboratory on modern standards. The results of blood tests, whether positive or negative, are kept confidential between the employee and the medical division except in the case of a person who refuses to take adequate treatment, in which case the department head is advised and the employee discharged. Persons suffering with syphilis are not

excluded from employment nor are employees in the organization discharged on this account, but continued employment is contingent upon the employee's willingness to take treatment. There are, however, four exceptions to this rule: (1) food handlers, (2) employees engaged in the handling of any materials which are used in foods or for the wrapping of foods, (3) employees exposed to lead compounds, (4) employees with evidence of neurosyphilis. It is surprising, interesting and regrettable that with so modern an approach to the problem on the part of an industrial organization, the inadequacy of knowledge and non-coöperativeness of physicians at large have brought the scheme to the point where its industrial sponsors consider the situation unsatisfactory. Gehrman summarizes with comment that demands exact quotation, for it is a genuinely tragic reflex of a situation probably of national extent, which more than any other single item in the whole venereal disease control program threatens the hope of the future:

"Most physicians demand prices for treatment that are beyond the means of the individuals and out of reasonable proportion to their incomes. Some physicians maintain these high prices despite the fact that they are receiving arsphenamine, neoarsphenamine, and bismuth free of cost from their State.

"Many physicians refuse to treat the referred cases, stating that no treatment is indicated, in spite of 4+ Kahn and Wassermann reactions although the cases have never received adequate treatment.

"Numerous physicians refuse to admit that their patients have syphilis (again in the face of 4+ Kahn and Wassermann reactions). This group denies the validity of blood tests and states that they have known their patients for years, and further know that these same patients could not have contracted syphilis without their (the doctors') knowledge.

"On several occasions the attending physician has sent a blood specimen to a private or State laboratory and the report has come back that the reaction is negative. In every instance the results obtained by the company laboratory have been corroborated by subsequent check, but the attending physician has not always admitted that the patient has syphilis.

"Many cases are discharged as having had sufficient treatment, after three to ten injections of neoarsphenamine without a heavy metal.

"Some are being treated with pills and nothing else.

"Treatment at the free clinics is very satisfactory but it is not always possible for employees to conform to clinic hours and in some places the clinics refuse to treat any patient who is employed. The evidence presented above indicates that the incidence of syphilis in industry is of sufficient extent to be well worth consideration both from the standpoint of public health and industrial risk. The problem of getting these cases adequately treated is extremely difficult, and the question arises, is it advisable for industry to assume the entire obligation of treating these cases?

"There is no question but that this work is well worthwhile, and there is no question about the adequacy of the treatment which the majority of these infected employees receive. But it does seem advisable for the industry to take over the entire management of these patients and thus insure to them continuous and proper treatment."

There can be no question in the minds of those who have followed the

venereal disease control movement for years that there exists in the United States at this time an extraordinary combination of the will to accomplishment and the means therefor. For the future to be as bright as many students believe to be possible, and all concerned hope will be the case, two elements are vitally essential. The first is an exceptional spirit of informed coöperativeness on the part of the medical profession and the second is a consistent and tactful regard for human nature as the great determining influence in conduct—for this, after all, underlies all problems of health.

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REFERENCES.

- (1.) Annual Report of the Chief Medical Officer of the Ministry of Health for the year 1935, H. M. Stationary Office, London, p. 215, 1936. (2.) Bartholomew, R. A.: J. Am. Med. Assn., 83, 172, 1924. (3.) Boas, H., and Gammeltoft, S. A.: Acta gynec. Scand., 1, 309, 1922; Arch. f. Gynäk., 128, 527, 537, 1926. (4.) Brumfield, W. A., and Smith, D. C.: Am. J. Pub. Health, 24, 576, 1934. (5.) Cabot, R. C.: Boston Med. and Surg. J., 193, 1245, 1925. (6.) Cannon, A. B., and Robertson, J.: J. Am. Med. Assn., 106, 2133, 1936. (7.) Carley, P. S.: Ven. Dis. Inf., 18, 21, 1937. (8.) Clarke, C. W.: A Report of the New York City Commission to Investigate the Prevention and Control of Syphilis in the Scandinavian Countries and Great Britain, Am. J. Syph. Gon. and Ven. Dis., 20, Pt. 2, July, 1932. (9.) Cole, H. N.: J. Am. Med. Assn., 107, 2123, 1936. (10.) Cole, H. N. (with Usilton, L. J., and Moore, J. E., et al.): (a) Ven. Dis. Inf., 17, 39, 1936; (b) Ibid., p. 91; (c) Ibid., 18, 97, 1937. (11.) Cumming, H. S., Hazen, H. H., Sanford, A. H., Senear, F. E., et al.: J. Am. Med. Assn., 104, 2083, 1935. (12.) Editorial: Ven. Dis. Inf., 16, 223, 1935. (13.) Exner, M. J.: Ibid., p. 59. (14.) Gehrmann, G. H.: Ibid., 17, 227, 1936. (15.) Gumpert, M.: Dermat. Wehnschr., 79, 852, 1924. (16.) Harrison, L. W.: Brit. J. Ven. Dis., 11, 69, 1935. (17.) Ingraham, L. B.: J. Am. Med. Assn., 107, 1990, 1936. (18.) Ingraham, L. B., and Stokes, J. H.: Ven. Dis. Inf., 18, 127, 1937. (19.) Ingraham, N. R.: Syphilis Epidemiology Applied: Fifteen Years Experience with Contact Tracing and Case Holding in New Jersey, Ibid. (in press). (20.) Källmark, H. J.: Eine statistische Untersuchung über Syphilis, Uppsala, Appelberg, 1931. (21.) Leland, H. N., Nelson, N. A., and Gorman, A. I.: New England J. Med., 203, 1200, 1930. (22.) McCord, J. R.: Am. J. Obst. and Gynec., 11, 850, 1926; J. Am. Med. Assn., 88, 626, 1927; 105, 89, 1935. (23.) McKneely, T. B.: Ven. Dis. Inf., 18, 179, 1937. (24.) Moore, J. E.: (a) Ven. Dis. Inf. (Suppl. 3, 1936), p. 84; (b) Ann. Int. Med., 10, 30, 1936; (c) Am. J. Syph. Gon. and Ven. Dis., 20, 91, 1936; (d) Ven. Dis. Inf. (Suppl. 2), p. 29, April, 1936; (e) Moore, J. E., Cole, H. N., O'Leary, P. A., Stokes, J. H., Wile, U. J., et al.: Ven. Dis. Inf., 13, 317, 351, 371, 389, 407, 1932; 14, 1, 1933. (25.) Morris, E. H.: New England J. Med., 209, 735, 1933. (26.) Munson, W. L.: Am. J. Pub. Health, 22, 134, 1932. (27.) Nelson, N. A. (a) New England J. Med., 208, 1153, 1933; (b) Am. J. Syph. Gon. and Ven. Dis., 20, 88, 1936; (c) Ibid., p. 448; (d) Ven. Dis. Inf., 17, 359, 1936; (e) New England J. Med., 215, 894, 1936; (f) J. Am. Med. Assn., 106, 105, 1936. (28.) O'Leary, P. A., Cole, H. N., Moore, J. E., Stokes, J. H., et al.: Ven. Dis. Inf., 18, 45, 1937. (29.) Ormsby, O. S.: J. Am. Med. Assn., 106, 1241, 1936. (30.) Parran, T. (a) Survey Graphic, 25, 405, 1936; (b) J. Am. Med. Assn., 109, 205, 1937; (c) Shadow on the Land, Reynal and Hitchcock, New York, 1937; (d) Readers Digest, 30, 21, 1937. (31.) Parran, T., Hazen, H. H., Mahoney, J. F., et al.: J. Am. Med. Assn., 109, 425, 1937. (32.) Parran, T., Hazen, H. H., Sanford, A. H., et al.: Ven. Dis. Inf., 18, 4, 1937. (33.) Pugh, J. H., Stokes, J. H., Brown, L. A., and Carnell, D.: Am. J. Syph., 14, 438, 1930. (34.) Ramsey, G. H.: Ven. Dis. Inf. (Suppl. 3), p. 73, Dec., 1936. (35.) Reinhard, F. O., and Fales, W. T.: J. Am. Med. Assn., 106, 1377, 1936. (36.) Schwerts, H.: Bruxelles med., 9, 1375, 1929. (37.) Smith, D. C.: J. Am. Med. Assn., 107, 784, 1936. (38.) Smith, D. C., and Brumfield, W. A.: Ibid., 101, 1955, 1933. (39.) Stokes, J. H.: (a) J. Soc. Hygiene, 21, 313, 1935; (b) Ven. Dis. Inf., 17, 315, 1936; (c) J. Am. Med. Assn., 107, 866, 1936; (d) Am. J. Syph. Gon. and Ven. Dis., 20, 231, 1936; (e) J. Am. Med. Assn., 108, 780, 1937. (40.) Stokes, J. H. (with Usilton, L. J.,

and Cole, H. N., Moore, J. E., et al.): *Am. J. Med. Sci.*, 188, 660, 669, 678, 1934. (41.) Stokes, J. H., and Usilton, L. J.: *Arch. Derm. and Syph.*, 35, 377, 1937. (42.) Stokes, J. H., Besançon, R. G., and Schoch, A.: *J. Am. Med. Assn.*, 96, 344, 1931. (43.) Stokes, J. H., Cole, H. N., Moore, J. E., et al.: (a) *Ibid.*, 102, 1267, 1934; (b) *Ven. Dis. Inf.*, 12, 55, 1931. (44.) U. S. Bureau of the Census: *Births, Stillbirths and Infant Mortality, Annual reports 1921-1933*. Washington, Government Printing Office. (45.) Usilton, L. J.: *Ven. Dis. Inf.*, 16, 147, 1935. (46.) *Ven. Dis. Inf.* (a) (Suppl. 3, 1936) Appendix D, Table 4; Appendix E, Fig. 2; (b) (Suppl. 3, 1936) Appendix D, Table 11, Appendix E, Fig. 5. (47.) Vonderlehr, R. A.: (a) *Ven. Dis. Inf.*, 16, 413, 1935; (b) *Ibid.* (Suppl. 3), p. 125, Dec., 1936. (48.) Vonderlehr, R. A., Bundesen, H. N., Moore, J. E., et al.: *Ven. Dis. Inf.*, 17, 1, 1936. (49.) von Düring, E.: *Mitt. d. deutsch. Gesellsch. 2. Bekamff. d. Geschlechtshr.*, 23, 59, 1925. (50.) White, P. D.: *Heart Disease*, New York, The Macmillan Company, 1931, p. 360. (51.) Wile, U. J.: *Ven. Dis. Inf.* (Suppl. 3), p. 103, Dec., 1936.

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ORIGINAL ARTICLES.

ROENTGEN THERAPY OF ACTIVE RHEUMATIC HEART
DISEASE.*

A SUMMARY OF ELEVEN YEARS' EXPERIENCE.

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RHEUMATIC fever is a chronic disease, of which the specific causative agent is, as yet, unknown. Its chief menace to health and life is involvement of the structures of the heart. The use of salicylate as a symptomatic remedy in the acute stages has long been accepted practice. Eradication of foci of infection, avoidance of colds and sore throats, and prolonged rest in a favorable environment are the methods of therapy commonly employed.

There are many cases in which activity of the rheumatic state continues over long periods of time, as indicated by low grade fever, leukocytosis and increase in the rate of sedimentation of the red blood corpuscles. Active lesions in the myocardium can be inferred by the persistence of tachycardia and by progressive alterations in the form of the electrocardiogram. For such patients, many months of rest in bed is essential. Some suffer intensely from attacks of cardiac pain.

In three previous communications¹ we have reported in detail the results of the treatment of rheumatic carditis by Roentgen irradiation of the heart. It was pointed out that Roentgen rays exert a favorable influence on various forms of low grade infection. On the basis of changes recorded in the contour of the electrocardiogram,

* Read at the Eastern Conference of Radiologists, New York City, January 29, 1937.

it was inferred that the lesions in the heart were affected. The improvement in the clinical condition of many patients shortly following exposure of the heart to the rays, and the relief of pain in a smaller group, warranted the conclusion that the effect exerted was beneficial. The mechanism by which these changes were brought about remained a matter of conjecture; it was suggested that, in some manner not understood, the reactivity of the cardiac tissues was altered.

It is now almost 12 years since the first patient was treated. Further experience, together with 2 favorable reports in the foreign literature,^{2,3} have strengthened our conviction that the method is worthy of continued trial. Certainly until a more direct mode of attack upon the cause of the disease is developed, it furnishes an added measure for shortening the required period of invalidism. These notes may be regarded as a report of progress.

Results After 11 Years. We have followed 48 patients with sufficient care to warrant including them in the analysis (Table 1); 36 are living; 12 have died. There was a wide range in the degree of severity of cardiac damage.

TABLE 1.—SUMMARY OF 48 CASES.*

<i>Living</i>	36	<i>Dead</i>	12
<i>Result:</i>		<i>Death occurred from</i> 6 weeks to 7½	
Improved	25	years after first radiotherapy was	
Unimproved	3	given	
Doubtful	8	<i>Average duration of life (from this</i>	
<i>With cardiac pain:</i>	8	time), 2½ years	
Relieved	6	<i>Temporarily improved</i>	7
<i>Duration of Follow-up:</i>		<i>With cardiac pain</i>	2
Less than 1 year	7	Relieved, 0 (both had aortic insuf-	
1 to 3 years	14	iciency)	
4 to 6 years	7	<i>Cause of Death:</i>	
7 to 9 years	4	Congestive heart failure	7
10 to 11 years	4	Strept. viridans endocarditis	3
<i>Number of Radiation Treatments:</i>		Pneumonia	1
4 to 25, during a period ranging		Not known	1
from 1 month to 1½ years.			
Average number per patient, 9			
Receiving 10 or more, 12 patients			

* We are indebted to Drs. D. W. Atehley and A. F. Anderson, of New York, and Dr. J. W. Coburn, of East Orange, N. J., for referring private patients for treatment.

Patients Still Alive. Of 36, 25 were regarded as improved by treatment; a direct relationship between betterment and therapy seemed apparent. Three were unimproved; in 8 cases, although recovery from the immediate attack ensued, there was no reason to believe that radiation played a rôle. Of 8 patients with cardiac pain, 6 obtained striking relief.

The duration of follow-up after the first irradiation ranged from less than 1 year to 11½ years. Fifteen patients have now been observed for more than 4 years, and 8 for more than 7 years.

The number of treatments given to an individual ranged from 3 to 25 (average 9); 12 cases received 10 or more. About half of the

patients experienced mild radiation reactions. In general, those receiving the larger number of treatments fared best; but this was not an invariable rule.

Patients Who Have Died. Of 12 cases, 7 died of congestive heart failure; 3 of streptococcus viridans endocarditis; 1 of pneumonia; and in 1 case, dying at home, the cause was not ascertained. Seven patients showed temporary improvement. But in 2 who had cardiac pain associated with a large aortic leak, no relief was obtained. Death occurred from 6 weeks to $7\frac{1}{2}$ years after treatment was initiated. The average duration of life, from this time to death, was $2\frac{1}{4}$ years.

Technique of Irradiation. This was described in previous papers and is repeated here, for convenience.

In giving the treatments the following factors were used: 200 Kv. (peak); 0.5 mm. copper plus 1 mm. aluminum filter; 50 cm. target skin distance. The field was made large enough to include the heart, using one field in front and one posteriorly. Approximately 60r as measured in air, without back-scattering, was applied to the front of the chest and from 100 to 125r to the back, depending upon the depth of the patient's thorax. The object was to distribute approximately 60r, as measured in air, throughout the heart area, corresponding to about $1/10$ of the old "erythema dose." If there was evidence of a systemic reaction to this dose the quantity of radiation was decreased. The treatments were given at intervals of 2 weeks for 4 sittings. Then a period of 1 to 3 months was allowed to elapse, and the series of 4 was repeated.

Effects of Irradiation on the Heart. Lesions in the heart have been described in laboratory animals and in humans after deep Roentgen irradiation. In our earlier papers ^{a,b} we have pointed out that the dosage employed by others to bring about harmful reactions in the myocardium and pericardium has been much larger than that used by us. Only one of our cases has been examined at necropsy after having received irradiation; a brief protocol follows:

Case Abstract. A girl, aged 17, received 9 radiation treatments during a period of 5 months. She died of acute cardiac insufficiency 24 hours after the onset of fulminating, bilateral maxillary sinusitis. Death occurred 1 year and 4 months after the final irradiation. The pathologic diagnosis was rheumatic endocarditis, mitral stenosis and insufficiency, tricuspid insufficiency, cardiac hypertrophy, thrombosis of the left auricle and right auricular appendage. Microscopically, there were numerous scars in the heart muscle and an occasional Aschoff body was found. According to the pathologist, there were no changes in the heart which could be ascribed to radiotherapy.

Comment. The difficulties of making a just appraisal of the therapeutic value of irradiation of the cardiac area are obvious. Rheumatic heart disease, untreated, runs a variable course, sometimes with long remissions. In children, 85% with active carditis have a recurrence within 3 years.⁵ Juvenile rheumatism shows a great tendency to relapse, with progressive damage to the tissues of the heart. In adults, the onset of myocardial insufficiency usually indicates that the termination of life is not far off; on the average,

death occurs within 3 years, during which the patient is partly or wholly incapacitated.¹

In those instances recorded as improved, there appeared to exist a relationship between treatment and result. Lowering of temperature, fall in heart rate, lessening of the sedimentation rate of the erythrocytes and, above all, general clinical improvement, served as guides. The relief of cardiac pain in some cases was striking. To those who choose to say that these effects might have occurred in the absence of irradiation, we can present no final proof. Our experience has convinced us that the method is useful in selected cases.

Certain special features deserve comment. In a number of patients, in bed for months with signs of smouldering rheumatic activity, evidence of the subsidence of carditis has appeared soon after Roentgen therapy was begun. Several, in spite of severely damaged and greatly enlarged hearts, have remained free from demonstrable active carditis for over 10 years, although they have suffered from occasional respiratory infections and have, at times, had rheumatic twinges in the joints. One woman with early mitral disease when first seen, has worked for 10 years as an occupational therapist without increase in signs or recurrence of symptoms. Another woman, now 28 years of age, recently went through a normal pregnancy 9½ years after irradiation therapy; there has never been a return of rheumatic activity. A woman of 37 with agonizing abdominal pain due, it was believed, to rheumatic aortitis of the abdominal aorta, received 16 treatments over the abdomen during a period of 1 year. She has been free from discomfort for almost 6 years. A private patient followed by one of us, a woman, aged 37, had been in bed, running a low grade fever for 8 months. The heart was moderately enlarged; the signs were those of mitral stenosis, without congestive failure. Tonsillectomy had been performed without benefit. During a period of 6 months she received 8 irradiations. After the first treatment, the temperature fell to normal. Signs of mitral stenosis, of course, persist. But for 5 years she has led a normal life, running her household and participating actively in social activities. There has been no recurrence of carditis.

On the basis of a small material, generalizations are not justified. But it is our impression that the low grade infections respond better to irradiation than the more acute types; and that patients with congestive heart failure are poor subjects for this form of therapy. Early cases, with minimal cardiac damage, obviously offer the best chance for inducing a favorable response. On the other hand, a large heart with good functional capacity, appears to react well. Of the patients with cardiac pain, those with aortic insufficiency have obtained no relief, whereas those without this valvular defect have been uniformly helped. This is readily understandable. In aortic regurgitation with a large leak, the coronary flow is diminished and discomfort is due largely to relative ischemia of the myo-

cardium. When pain is due to rheumatic lesions in the heart muscle, an altered reaction of the cardiac tissues may aid in bringing about their dispersion.

Summary. 1. Forty-eight patients with rheumatic heart disease have been treated by Roentgen irradiation of the heart and have been observed during the past $11\frac{1}{2}$ years.

2. In a considerable number the evidence indicated that radiation therapy exerted a favorable effect upon the lesions in the heart and upon the course of the disease. Those receiving the larger number of treatments, as a general rule, fared best.

3. Irradiation relieved cardiac pain in patients who did not have aortic insufficiency.

4. No harmful effects were noted. Unpleasant radiation reactions appeared in about half the cases.

5. Cases with low grade activity and without signs of congestive heart failure appear to be most benefited.

6. The manner in which improvement is initiated is not known. It is believed to be due to an altered response of the cardiac tissues induced by the rays.

7. Roentgen irradiation of the heart, in the present state of knowledge concerning rheumatic fever, deserves a place as a therapeutic measure in properly selected cases of active carditis.

REFERENCES.

- (1.) DeGraff, A. C., and Lingg, C.: *Am. Heart J.*, 10, 459, 1935. (2.) Jegorow, B.: *Strahlentherapie*, 52, 97, 1935. (3.) Kohan, B. D., Bunin, E. I., and Tscherjatschukin, S. F.: *Ztschr. f. Kreislaufforsch.*, 27, 492, 1935. (4.) Levy, R. L., and Golden, R.: (a) *Am. J. Roentgenol. and Rad. Ther.*, 18, 103, 1927; (b) *Am. Heart J.*, 4, 127, 1928; (c) *Am. J. Roentgenol. and Rad. Ther.*, 29, 79, 1933. (5.) Roth, I., Lingg, C., and Whittemore, A.: *Am. Heart J.*, 13, 36, 1937.

CLINICAL OBSERVATIONS ON THE DYNAMICS OF VENTRICULAR SYSTOLE.

IV. PULSUS ALTERNANS.*

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ALTHOUGH pulsus alternans is a well known sign clinically and the subject of voluminous experimental and clinical investigation, the cause of the alternate large and small beats is still the subject of controversy. The field has been extensively reviewed by Poumail-

* Based on a study made on 5 patients taken from the medical wards of the City and Mt. Sinai Hospitals of Cleveland, Ohio.

loux⁹ and by Kisch.⁷ Since its first recognition by Traube,¹¹ it has been encountered in a variety of conditions, and when persistent, it has been regarded as a sign of grave prognosis. It may be a temporary condition in intoxications, in rapidly beating hearts such as paroxysmal tachycardia and in disturbances of rhythm, such as premature systoles. It may be a more or less permanent pulse phenomenon in myocardial degeneration, especially when associated with hypertension. It is then often associated with intra-ventricular block and gallop rhythm.

The definiteness of the clinical facts form a sharp contrast to the confusion regarding the causation of the phenomenon. The confusion has arisen in part because there is an apparent contradiction between the law of "all or none" response of the heart and the alternate size of the heart's response. The theories concerning the mechanism of pulsus alternans are numerous, but they can be grouped as shadings of two major concepts:

A. During systole some of the muscle fibers of the ventricles fail to contract because a prolonged refractory state in certain regions leads to localized blocks. One group of investigators maintains that this dropping out of muscle groups is confined to the small beats (Gaskell² and Hering⁴), while another group maintains that some muscle groups fail to contract in every systole, the number failing in the small beats being greater than in the large ones (Mines⁸).

B. Initiation and perpetuation of alternation is due in whole or in part to alternating dynamic changes of the heart set off by fluctuations in the circulation which are occurring constantly. The exact cause and effect relationship is not agreed upon by the exponents of this view (Wenckebach,¹² Frederique,¹ Straub,¹⁰ Kahn⁵ and Wiggers^{13b}).

In view of this situation, it seemed to us that there was a need of careful study of the influence of alternation on the dynamics of ventricular systole in man utilizing the more accurate optical registration methods.⁶ The present report is based on observations made on 5 patients with pulsus alternans. Changes in the duration of the phases of systole and diastole can be measured in man and in this way would be of help in correlating the experimental observations of Kahn,⁵ Straub¹⁰ and Wiggers^{13b} with the clinical observations of Wenckebach.¹² Wiggers, for example, found that in experimental pulsus alternans the duration of systole in the large beats was noticeably longer than that of the small beats, and this was true also of the duration of the ejection phase. The isometric contraction phase, however, varied in just the reverse direction, and what is more important, so did the duration of diastole.

Case Reports. CASE 1.—J. M. (C. C. H.), a white male, aged 22, presented the picture of renal insufficiency associated with chronic glomerular nephritis. During his stay in the hospital, he developed pulsus alternans that

persisted until death. Records were taken on February 16, 1922, when his blood pressure was slightly elevated. The electrocardiogram showed normal sinus rhythm without any conduction disturbance (Fig. 1). The three heart sounds alternate slightly concordantly with the pulse; it is also to be noted that the small beats rise from a higher level than do the large beats—the higher level signifying a relatively greater arterial distention and a relatively greater diastolic blood pressure.

Shortly after this record was taken, exitus occurred, and the postmortem examination revealed beside the usual pathologic picture of chronic glomerular nephritis a moderately enlarged heart without valvular defect.

Table 1 was constructed from the measurements of 19 consecutive beats in two plates. The duration of each preceding diastole will be seen in Column II. The duration of this phase is variable but bears no definite relation to the height of the succeeding beats (Compare Columns I and II). Total systole varied little from beat to beat, although total systole due to the myocardial failure was shorter than the normal at corresponding rates.

TABLE 1.—CASE 1. ANALYSIS OF 17 BEATS.

I. Height of beat subclavian art. pulse mm.	II. Duration of previous diastole sec.	III. Duration of total systole sec.	IV. Duration of isometric contraction period sec.	V. Duration of ejection phase sec.	VI. Pulse gradient mm./sec.
PLATE 1*					
26	0.215	0.041	0.174	149
19	0.310	.212	.051	.161	117
22	.310	.217	.040	.177	142
19	.313	.215	.050	.163	116
26	.316	.209	.038	.171	152
18	.316	.212	.050	.162	111
27	.318	.230	.045	.185	146
18	.306	.221	.061	.160	112
29	.323	.211	.034	.177	108
PLATE 2*					
17	0.204	0.060	0.144	118
30	0.315	.201	.052	.149	201
19	.318	.192	.055	.137	138
31	.322	.199	.047	.152	204
22	.314	.197	.053	.144	152
28	.316	.191	.037	.154	182
19	.329	.194	.056	.138	135
30	.317	.190	.033	.157	190

* Heart rate 113 per min.

The isometric contraction period shows a striking alternation in its duration. Without exception this phase is longer in the smaller beats than in the larger beats. The difference between the duration of the isometric phase in successive beats ranged from 0.003 to 0.027 sec. The ejection phase also shows alternation, but the longer periods occur in the larger beats. Measurements of this phase in successive beats show a difference of 0.005 to 0.025 sec. The relative heights of the beats are given in Column I. The pulse gradient determined as described in a previous report⁶ is greater in the larger beats.

CASE 2.—B. B. (C. C. H. No. 416), a negro male, aged 44, had congestive heart failure secondary to chronic hypertension (B.P. 194/180/130 on 6-29-22), with Cheyne-Stokes respiration. The patient was under observation for 2 years, during which period he persistently showed pulsus alternans of varying degree. Records were taken on several occasions. The electro-

cardiograms showed a definite prolongation of the *P-R* interval (Fig. 2). Alternation of the heart sounds also occurred, the first and second sounds being more intense in the large beats. The third heart sound, which by its position is attributed to auricular systole, is more intense in the cycle preceding the small beat (Fig. 2). In Table 2 are tabulated the measurements of 21 consecutive beats obtained from records on three different occasions. Previous diastole shows no definite alternation except on one occasion (9-26-22) where the longer diastoles precede the large beats. The variations in the durations of this phase are so slight as to be inconsequential. Total systole, which is shorter than the normal at corresponding rates, shows no consistent alternation. The isometric period was mostly prolonged in the smaller beats (0.002-0.018 sec.). Ejection, on the other hand, is abbreviated in the smaller beats.

TABLE 2.—CASE 2. ANALYSIS OF 21 BEATS.

I. Height of beat subclavian art. pulse mm.	II. Duration of previous diastole sec.	III. Duration of total systole sec.	IV. Duration of isometric contraction period sec.	V. Duration of ejection phase sec.	VI. Pulse gradient mm/sec.
5/23/22*					
8	0.184	0.060	0.124	64
12	0.335	.195	.069	.126	95
8	.331	.195	.062	.133	60
12	.339	.196	.059	.137	87
9	.330	.197	.072	.125	72
12	.337	.200	.066	.133	89
9	.331	.199	.067	.132	68
11	.343	.190	.053	.137	80
9	.342	.191	.071	.120	75
5/26/22†					
10	0.412	0.230	0.048	0.182	55
9	.395	.263	.076	.187	48
10	.437	.242	.052	.190	52
10	.453	.240	.054	.186	54
12	.453	.247	.053	.194	62
10	.456	.237	.049	.188	53
9/26/22†					
15	0.218	0.079	0.139	107
17	0.460	.210	.069	.141	120
14	.452	.213	.070	.143	98
18	.465	.217	.068	.139	139
16	.457	.211	.071	.140	114
18	.460	.217	.065	.152	118

* Heart rate 110.

† Heart rate 84.

CASE 3.—J. Wa. (C. C. H. No. 76525), a negro male, aged 55, was observed for several years during successive attacks of cardiac failure due to preëxisting vascular hypertension. Pulsus alternans was repeatedly observed but of varying degree. Records taken on May 17, 1922 (B.P. 130/110), of which Figure 3 is an example, show an alternation of the second heart sound associated with the alternating pulse, the second heart sound of the large beats being the more intense and longer in duration. Electrocardiograms show a prolonged *P-R* interval (Fig. 3). The measurements of 13 successive beats are tabulated in Table 3 in a manner similar to the preceding tables. Study of this table shows no constant relation between diastolic length and the size of the succeeding beat (Columns I and II); total systole shows no constant alternation (Column III), but the isometric

period is prolonged, the ejection shortened and the pulse gradient decreased in the smaller beats.

TABLE 3.—CASE 3. ANALYSIS OF 13 BEATS.

I. Height of beat subclavian art. pulse mm.	II. Duration of previous diastole sec.	III. Duration of total systole sec.	IV. Duration of isometric contraction period sec.	V. Duration of ejection phase sec.	VI. Pulse gradient mm/sec.
PLATE 1*					
10	0.422	0.197	0.058	0.139	72
7	.418	.203	.068	.135	51
10	.416	.199	.059	.140	71
8	.420	.193	.062	.131	61
9	.425	.189	.065	.124	72
7	.413	.208	.071	.137	50
PLATE 2*					
13	0.199	0.065	0.134	97
9	0.417	.190	.071	.119	76
12	.417	.207	.065	.142	83
10	.422	.190	.065	.125	80
12	.422	.199	.063	.136	88
9	.427	.192	.075	.117	77
111	.439	.189	.069	.120	92

* Heart rate 97.

TABLE 4.—CASE 4. ANALYSIS OF 14 BEATS.

I. Height of beat subclavian art. pulse mm.	II. Duration of previous diastole sec.	III. Duration of total systole sec.	IV. Duration of isometric contraction period sec.	V. Duration of ejection phase sec.	VI. Pulse gradient mm/sec
PLATE 1*					
25	0.215	0.050	0.164	152
21	0.374	.209	.070	.139	151
29	.404	.196	.031	.165	182
20	.377	.204	.071	.133	150
30	.402	.196	.049	.147	204
23	.389	.201	.072	.129	178
29	.390	.216	.052	.164	176
PLATE 2*					
24	0.214	0.074	0.140	171
37	0.411	.193	.052	.141	262
23	.394	.192	.084	.108	213
39	.405	.199	.054	.145	269
25	.377	.218	.078	.140	178
38	.409	.196	.046	.150	253
25	.371	.210	.073	.137	183

* Heart rate 100.

CASE 4.—J. Wi. (C. C. H. No. 76834), a negro male, aged 52, likewise suffered from congestive cardiac failure consequent to vascular hypertension (B.P. 220/140). During his failure, he developed Cheyne-Stokes breathing, and during his last admission, he developed pulsus alternans. The electrocardiograms showed that complete block coexisted with an unusually fast ventricular rate (100 per min.). The auricular rate was 150 (Fig. 4). Postmortem examination showed a considerably hypertrophied heart and a hemorrhage in the main stem of the bundle of His. From Table 4 it will be seen that the larger beats are preceded by slightly longer

diastoles, and the changes in systole and its phases are in accord with those of the preceding table. Associated with the alternating pulse is a concordant alternation of the second heart sounds (Fig. 4).

TABLE 5.—CASE 5. ANALYSIS OF 34 BEATS.

I. Height of beat subclavian art. pulse mm.	II. Duration of previous diastole sec.	III. Duration of total systole sec.	IV. Duration of isometric contraction period sec.	V. Duration of ejection phase sec.	VI. Pulse gradient mm/sec.
PLATE 1*					
9	0 217	0.081	0.136	66
17	0.386	.237	.066	.171	99
7	P.S. .104	.201	.051	.150	47
33	.619	.225	.052	.173	191
1	.428	.227	.154	.073	14
19	.354	.247	.081	.165	109
7	.379	.219	.097	.122	57
16	.373	.205	.057	.148	108
10	.398	.203	.068	.135	74
PLATE 2*					
11	0.276	0.129	0 147	74
18	0.317	.276	.116	.160	112
11	.324	.261	.113	.148	74
21	.363	.279	.119	.160	131
13	.296	.310	.156	.154	84
17	.300	.291	.131	.160	106
14	.331	.287	.130	.157	89
2	P.S. .208	.241	.149	.092	21
34	.505	.254	.077	.177	192
PLATE 3*					
23	0.262	0.092	0 170	135
9	0.339	.302	.152	.150	60
15	.296	.261	.104	.157	95
12	.325	.329	.169	.151	79
16	.278	.289	.130	.159	100
12	.327	.299	.145	.154	78
15	.294	.284	.119	.165	91
5	P.S. .066	.234	.104	.130	38
36	.608	.206	.037	.169	213
PLATE 4*					
12	0.281	0.155	0.126	95
8	0.336	.287	.170	.117	68
10	.342	.270	.145	.125	80
8	.345	.260	.112	.148	54
13	.356	.258	.099	.159	82
1	P.S. .055	.261	.207	.054	19
25	.652	.224	.054	.170	147

* Heart rate 100.

P.S. = Premature systole.

CASE 5.—J. Pol. (Mt. S. H. No. D. 1504), a white female, aged 50, had signs of early cardiac failure associated with vascular hypertension (B.P. 220/194/140). Pulsus alternans and premature ventricular beats were present. The alternation was most noticeable during heart failure. Electrocardiograms taken on April 7, 1924, showed the common type of bundle branch block unassociated with a prolongation in the P-R interval (Fig. 5). The concordant alternation of the second heart sound is also shown in

Figure 5. In Table 5 a slight alternation is seen at times in the duration of previous diastole (Column II), the taller beats succeeding shorter diastoles. There is an inconstant alternation of total systole, the shorter systoles occurring in the large beats. The alternation of the isometric period, ejection phase and pulse gradient are in keeping with the findings in the previous 4 patients.

Discussion of Results. The 5 cases of pulsus alternans detailed above consistently show associated with the alternation of the pulse, alternation in the intensity of the heart sounds, in the duration of the isometric and ejection phases and in the pulse gradient. The duration of total systole and of previous diastole showed no consistent alternation. While diastole occasionally alternated in duration, the changes were so slight as have little effect on ventricular filling. If diastole does exert an influence on filling, then this influence must be due to alternating changes in the duration of the isometric relaxation, rapid inflow or auricular systolic phases. In the present series we did not measure the duration of the diastolic phases which should be the subject of further clinical investigation.

The concordant alternation of heart sounds, especially the second sound, was a striking phenomenon in this series. The second sound was less intense in all cases and shorter in duration in 1 case (Case 3) in the smaller beats. A third heart sound was recorded in 2 cases. In one (Case 1) it occurred as a normal third heart sound during the rapid inflow phase. In the other (Case 2) it was evidence of augmented auricular activity accompanied by prolongation of the $P-R$ interval. In both instances there was alternation of the third sound, it being more intense in the diastoles preceding the small beat.

This alternation of the sounds substantiates in man the observations of Wiggers made on animals^{13a} that the intensity of the sound varies with the height of the intravascular tension.

The alternation of the isometric and ejection phases was discordant—in the small beats the isometric phase was relatively prolonged, while ejection was relatively shortened. In the large beats the reverse occurred; *i. e.*, the isometric phase was shortened and ejection prolonged. The fact that these phases altered in opposite directions explains the relative constancy of the duration of total systole.

The pulse gradient alternated concordantly with the size of the pulse, being less rapid in the smaller beats than in the large ones.

No alternation in the electrocardiograms was recorded in our series, although conduction changes were present in 4 cases (compare this with the reverse situation reported by Hamburger, Katz and Saphir³).

Interpretation of Results. Our results do not exclude the possibility that changes in refractory phase leading to alternating localized block may be the underlying mechanism of pulsus alternans. In

fact, the diverse forms of cardiac alternans and its varying manifestations can best be unified on such a basis.³ In simplest terms, pulsus alternans would represent various forms of localized 2:1 intraventricular (intraauricular or $A-V$) block. Such a condition, when operating in the left ventricle, could give rise to the dynamic changes described in the literature and the changes found by us in amplitude and slope of the pulse and in the duration of the systolic phases. On the other hand, our results do suggest that these dynamic changes could help to maintain the condition once it is initiated.

There is no doubt from past clinical experience and animal experimentation that pulsus alternans at slow heart rates indicates a badly damaged heart, and even in tachycardias this is true to a certain extent. In fact, it is probably safe to say that the seriousness of the permanent (as contrasted with the transient) damage to the heart varies: *a*, inversely with the rate of the heart; *b*, directly with the ease with which premature systoles, respiratory effort and marked sinus arrhythmia set it off; and, *c*, directly with the duration of its persistence following such precipitating factors.

In analyzing the possible rôle of dynamic changes in maintaining pulsus alternans, it is beside the point to argue that such dynamic changes can be brought about by 2:1 localized intraventricular block. It is much better, we believe, to see what the dynamic changes are and to examine whether or not they could lead to a perpetuation of the alternans *per se*.

From our results it is evident that alternation in the duration and force of ventricular systoles is not the result of alternation in the duration of diastole. In fact, Case 5 shows large beats following shorter diastoles and small beats after the longer diastoles. This is different from the experimental observations of Wiggers^{13b} who found alternating changes in diastole. The possibilities exist, however: *a*, that the phases of diastole are changed alternately to permit more filling time before the large beat and less filling time in the small beat as postulated by Straub;¹⁰ *b*, that the gradient of filling even with the filling time constantly alternates; and, *c*, that the auricular contribution itself may alternate and so make the total ventricular filling alternate also. Alternations in total filling need not be invoked, however, to explain differences in initial volume and tension of the left ventricle, since it stands to reason that the systolic residue will alternate, being greater after the small beat than the large. This is the view which Wenckebach¹² upheld. The work of Wiggers and Katz¹⁴ has shown that such changes in initial volume and tension determine the character of the beat that follows, and our studies have shown that this also applies in man.⁶ These experimental and clinical studies indicate that of all the variables initial volume and tension have the greatest influence on the dynamics of systole.

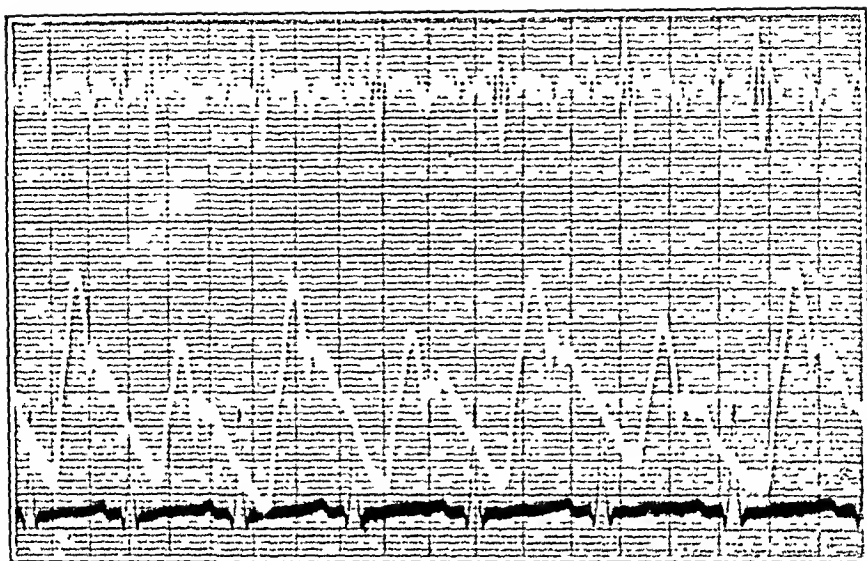


FIG. 1.—Simultaneous record of heart sounds (upper curve), subclavian arterial pulse (middle curve), and electrocardiogram, Lead II (bottom curve) in a patient with pulsus alternans (Case 1). I, 1st heart sound; II, 2d heart sound; III, 3d heart sound. Time in this and subsequent figures in fifths of a second.

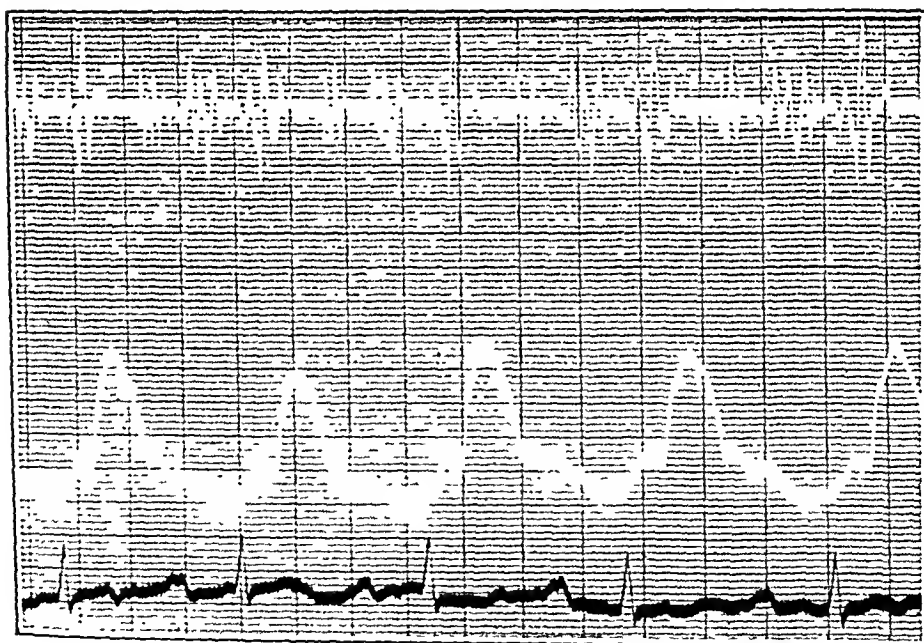


FIG. 2.—Record of Case 2. Items as in Figure 1.

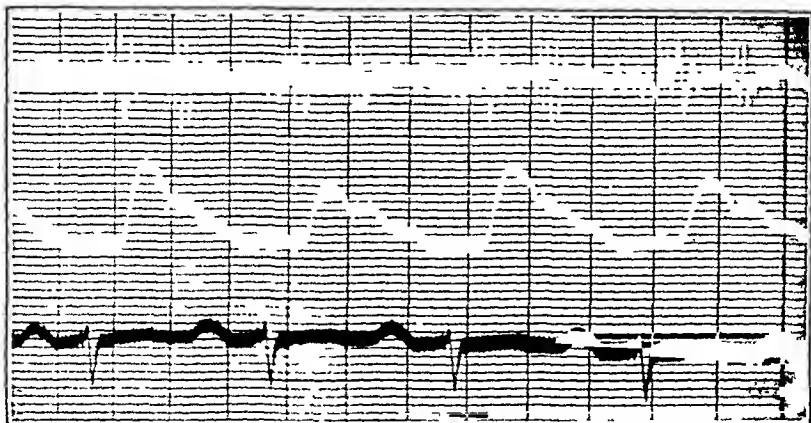


FIG. 3.—Record of Case 3. Items as in Figure 1.

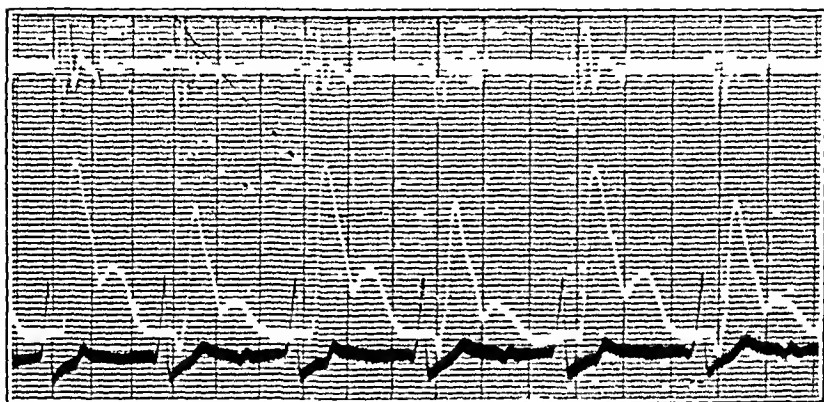


FIG. 4.—Record of Case 4. Items as in Figure 1. No 3d heart sound.

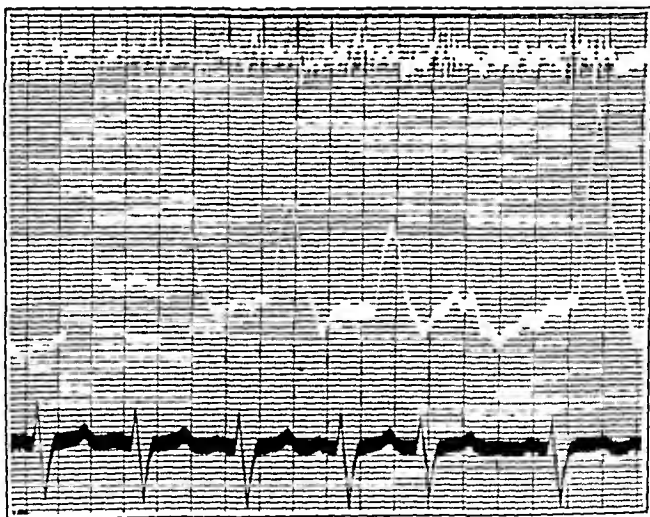


FIG. 5.—Record of Case 5. Items as in Figure 1. No 3d heart sound.

Assuming the above to be true, let us follow the changes in dynamics from beat to beat. Starting with a small beat, whatever its cause, with its reduced ejection rate and shortened ejection time we may conclude that the amount of blood ejected is reduced; consequently, there is an increased systolic remainder. This results in an increased initial volume and tension which explains the dynamics of the next beat, its magnitude, its rate of contraction and the duration of its systolic phases. Because the residue is large, the systole of the damaged heart empties it beyond the normal, and consequently, the residue for the succeeding beat is decreased beyond the normal and a small beat follows. This cycle of events continues for a variable time. Another factor which probably helps to accentuate this alternation is the change in diastolic pressure (the resistance to emptying), which is less in the diastole preceding the large pulse than in the one preceding the small pulse. Diastolic pressure therefore tends to hinder the emptying of the small pulse, permits a greater emptying of the large pulse and thereby tends to perpetuate the overswinging of the systolic remainder. This cycle of events may continue more or less indefinitely. The importance of initial tension and volume is further supported by the evidence given in Case 4 where large beats followed an effective auricular contraction, and small beats followed diastoles without auricular contributions.

Alternation may be initiated with a large pulse following an extrasystole, since the latter dynamically has the same effect as the small pulse of an alternans. A sudden change in rhythm may likewise initiate alternations in the initial tension and diastolic volume of the ventricle. This phenomenon may be started by marked variations in the depth of breathing such as occur in dyspnea and Cheyne-Stokes breathing. These also operate dynamically in the same manner as outlined above. There are thus several possible circulatory changes present in all cases which can initiate alternation in initial tension and volume.

We wish to make it clear that we have not proved that dynamic changes of one beat alone produce the dynamic changes in the next beat and so perpetuate pulsus alternans, nor have we proved that circulatory changes initiate pulsus alternans mechanically. The evidence we present, however, strongly suggests that such dynamic factors may help to initiate and perpetuate pulsus alternans.

Summary. The dynamics of systole in 5 clinical cases of pulsus alternans were studied by optical registration methods. The following conclusions were reached:

1. The alternation in the size of the pulse is accompanied by concordant alternations in the heart sounds, the gradient of the pulse and the duration of ejection, and by a discordant alternation in the duration of the isometric period. The duration of total systole showed no alternation.

2. No alternations were found in the electrocardiograms in this series, although conduction disturbances were present in 4 of the cases.

3. The duration of diastole did not vary consistently and was so small as to be without significance in explaining the alternation of the pulse volume.

4. In the case with complete heart block the pulsus alternans is attributed to contribution of auricular stimuli in alternate diastoles.

5. The evidence presented in this report, when correlated with previous studies of the dynamics of systole, supports the view that changes in initial volume and tension such as follow extrasystoles, sudden changes in rhythm and in respiration (so often present in alternation) can help to initiate the phenomenon of pulsus alternans. Once established alternate variations in systolic residue occur which alternately increase and decrease the initial tension and volume and so help to perpetuate the phenomenon. It is not denied that changes in the refractory phase are important in initiating and perpetuating pulsus alternans, but it is emphasized that the changes in initial tension and volume are likewise important.

REFERENCES.

- (1.) Fréderique, L.: *Archiv. f. ges. Physiol.*, 151, 108, 1913. (2.) Gaskell, W. A.: *Phil. Trans. Roy. Soc.*, 173, 993, 1882. (3.) Hamburger, W. W., Katz, L. N., and Saphir, O.: *Trans. Assn. Am. Phys.*, 50, 310, 1935; *J. Am. Med. Assn.*, 106, 902, 1936. (4.) Hering, H. E.: *Ztschr. f. Exp. Path. u. Therap.*, 7, 363, 1909. (5.) Kahn, R. H.: *Arch. f. ges. Physiol.*, 140, 471, 1911; 181, 65, 1920. (6.) Katz, L. N., and Feil, H. S.: *Arch. Int. Med.*, 32, 672, 1923; Feil, H. S., and Katz, L. N.: *Ibid.*, 33, 321, 1924. (7.) Kisch, B.: *Der Herzalternans*, Steinkopff, Leipzig, 1932. (8.) Mines, G. R.: *Proc. Cambridge Phil. Soc.*, 17, 34, 1913. (9.) Poumailloux, M.: *Le Pouls Alternant*, Masson & Cie, Paris, 1930. (10.) Straub, H.: *Deutsch. Archiv. f. klin. Med.*, 123, 403, 1917. (11.) Traube, L.: *Berl. klin. Wchnschr.*, 9, 85, 1872. (12.) Wenckebach, K. F.: *Ztschr. f. Klin. Med.*, 44, 218, 1910. (13.) Wiggers, C. J.: (a) *Arch. Int. Med.*, 24, 471, 1919; (b) *Contrib. to Med. Sci.*, dedicated to A. C. Warthin, p. 65, 1927, Ann Arbor, George Wahr. (14.) Wiggers, C. J., and Katz, L. N.: *Am. J. Physiol.*, 58, 439, 1922.

SUPPURATIVE PLEURITIS COMPLICATING PULMONARY INFARCTION IN CONGESTIVE HEART FAILURE.

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ALTHOUGH it is widely recognized that pulmonary infarction accompanied by a serous effusion frequently occurs in congestive heart failure, it appears to be less well known that sterile pulmonary

embolism and thrombosis may be followed by infection and suppuration of the hemorrhagic infarct with pleural extension and suppurative pleuritis.^{1,3-6} We are of the opinion that this occurs not uncommonly, for we have encountered 4 instances of this complication at necropsy in Bellevue Hospital during the past 3 years. Clinically, it is not always possible to decide whether infection of the infarct is spontaneous and of bronchiogenic origin, or whether it is attributable to contamination of the pleural space during thoracentesis performed for the initially clear and sterile effusion of pulmonary infarction, which usually precedes the suppurative pleuritis.

We are reporting the following cases from the Third Medical and Psychiatric Divisions of Bellevue Hospital, because they present morphologic evidence that the suppurative process in the pleura follows infection and suppuration of the infarcts with extension to the pleural space.

Case Reports. CASE 1.—T. H., a 47-year-old expressman, was admitted on January 19, 1934, for dyspnea and pain in the left chest. Eight weeks earlier he had experienced a sudden, severe substernal pain, which was followed by increasing dyspnea, cough productive of rusty streaked sputum and orthopnea. Three weeks before admission a severe sharp pain appeared in the left axilla.

Physical examination revealed an acutely and chronically ill white male, dyspneic, orthopneic, cyanotic. There were signs of fluid at the left base. The apical impulse was not palpable, a gallop was audible, the rate 120, the blood pressure 108/90. There were no palpable abdominal viscera, no edema or clubbing of the extremities.

The temperature was 102° F., the white blood count 22,850 with 89% granulocytes. The Wassermann reaction was negative, the blood culture sterile, and the sputum negative for tubercle bacilli.

The following day 2 liters of serosanguinous fluid were removed from the left chest. Dyspnea was diminished but signs of consolidation persisted in the axilla. The pleural fluid was sterile on culture; it contained many neutrophils and red blood cells but no organisms were visible on microscopic examination. On January 23 another thoracentesis of the left chest yielded 240 cc. of similar serosanguinous fluid. Pitting edema of the ankles, a palpable liver and icterus were soon noted. The initial and all subsequent electrocardiograms showed sinus tachycardia and left bundle branch block.

On January 28 symptoms and signs of a pulmonary infarct in the right lower chest appeared (Fig. 1). On February 8 the signs of sudden embolic closure of the left brachial artery were noted, but these soon subsided without gangrene. Evidence of fluid at the right base indicated thoracentesis on February 23, which yielded 500 cc. of serosanguinous fluid, sterile on culture. This was repeated on February 27 and fluid of identical character was obtained. On March 8 another tap of the right chest was performed and 175 cc. of thick foul pus were obtained, which on culture yielded many diphtheroids and a few isolated streptococcus hemolyticus colonies. The patient appeared prostrated with a persistently high fever and leukocytosis. Surgical drainage was thought inadvisable because of his poor general condition. Death occurred on March 16, 1935.

At necropsy (few hours after death), both lungs were found expanded and bound by dense fibrous adhesions to the parietal pleura. The pleura over the right lung measured almost a centimeter in thickness. Thick yellowish purulent fluid was encapsulated at both bases. Six wedge-shaped

infarcts were found in the left lung and a similar number in the right. The central portions of most of the infarcts appeared necrotic.

Microscopic sections of the infarcts revealed areas of hemorrhagic infarction in various stages of resolution, necrosis, organization and suppuration. In several sections the infarcted zones appeared as necrotic amorphous debris surrounded by zones of dense neutrophilic infiltration and organization. The arteries were plugged by recent and organizing thrombi and the pleural membrane was thickened by an organizing purulent exudate. Numerous rods and a few isolated cocci were demonstrated within the necrotic infarcts, as well as in the pleural exudate, in the Gram-Weigert sections.

The final anatomic diagnosis was: Chronic bilateral suppurative pleuritis with encapsulated empyema, multiple pulmonary infarcts with necrosis and suppurative pneumonitis, multiple pulmonary arterial thrombosis and embolization, hypertrophy and dilatation of the heart, coronary atherosclerosis, organized thrombus of the right coronary and anterior descending branch of the left coronary artery, old myocardial infarcts, mural thrombosis of the right and left ventricles and the right auricular appendage, arteriolar nephrosclerosis, old infarct of the left kidney, chronic passive congestion of the liver.

Summary of Case 1. A 47-year-old arteriosclerotic cardiac suffered myocardial infarcts which were accompanied by mural thrombi in both ventricles and in the right auricular appendage. Evidence of multiple pulmonary infarcts with pleural effusion appeared, and thoracentesis yielded a sterile serosanguinous fluid which was followed, after repeated taps, by the appearance of foul pus containing diphtheroids and hemolytic streptococci. Necrosis, infection and suppuration of the pulmonary infarcts were demonstrable at necropsy.

CASE 2.—J. A., a 45-year-old male, was admitted to the hospital on November 21, 1934. It was learned that he was admitted to another hospital on February 26, 1934, because of precordial pain, of 12 days' duration, which radiated to the left shoulder and arm. Clinical and electrocardiographic evidence of coronary occlusion and myocardial infarction were found. A Roentgen plate taken soon after entry into that institution, showed a patch of consolidation at the left base which was interpreted as a pulmonary infarct. He improved and was discharged on April 11, 1934, but reentered the same institution in May 17, 1934, because of the recurrence of precordial pain, cough, weakness and dyspnea. He remained on their wards in congestive heart failure, until November 21, 1934 when he became mentally disturbed and was transferred to Bellevue Hospital.

On examination, he appeared dyspneic, orthopneic, and cyanotic. There were râles at both bases and signs of a left pleural effusion. The heart sounds were distant, the blood pressure 100/90. On November 26 blood tinged expectoration was noted, and physical and roentgenologic signs of consolidation in the right upper lobe, with pleuritis and fluid at the right base, were obtained. The temperature rose to 102° F., the white blood count to 19,400 with 96% granulocytes. Thoracentesis of the right chest yielded 75 cc. of serosanguinous fluid. Some air was put in after the tap to secure better visualization of the lung field, and the Roentgen ray plate showed breaking down of the area of consolidation in the right upper lobe, and a fluid level at the base (Fig. 2). Death occurred the following day, December 4, 1934.



FIG. 1.—Multiple areas of density, particularly at the base of the right lung. There is enlargement of the heart.



FIG. 2.—Multiple areas of excavation in the right upper lung field. A fluid level is visible at the right base (air was introduced for better contrast study).

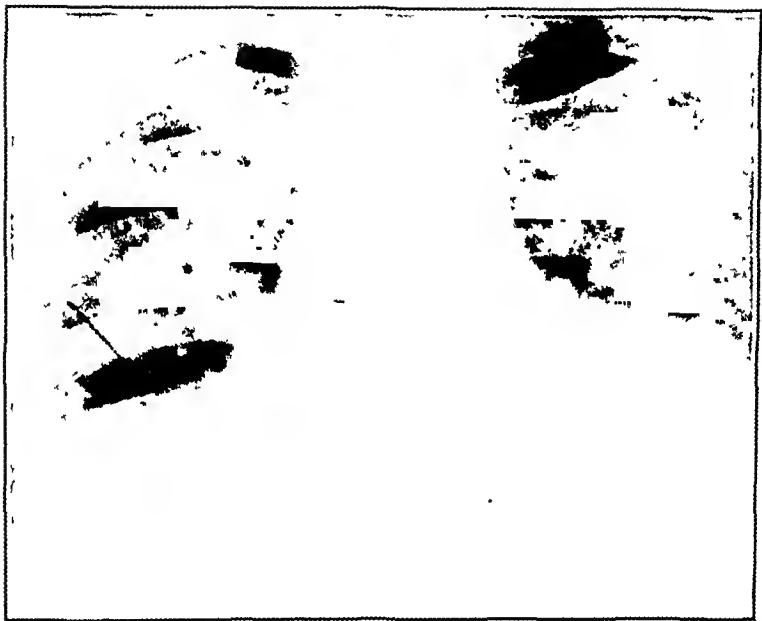


FIG. 3.—Changes of chronic passive congestion and a fluid level on the left (air was introduced for contrast after the tap). A patch of density is visible above the fluid level.

At necropsy, performed 6 days after death, the left pleural cavity contained about 225 cc. of clear serous fluid. In the lower half of the right pleural sac was an encapsulated cavity, lined by a thick purulent membrane and filled with thick purulent material. A large area in the posterior aspect of the right upper lobe appeared necrotic, and within it was a cavity about 6 cm. in diameter, limited from the pleural space by a thin shell of friable lung tissue. The pleural surface of the wall of the cavity showed a fibrinous membrane which extended downward to become continuous with the pyogenic membrane over the right lower lobe. The major branches of the pulmonary artery to the right upper lobe were plugged with organizing thrombi which extended to the edge of the necrotic area.

Microscopic sections through the right upper lobe showed the cavity to be lined by necrotic infarcted lung. In some areas the outlines of the necrotic alveolar walls were still discernible and the alveolar spaces were filled with hemolyzed red cells and pigmented macrophages. Elsewhere the wall consisted of amorphous necrotic debris. Surrounding the necrotic wall there was dense infiltration by polymorphonuclear leukocytes with abscess formation. A narrow rim of young granulation tissue and organizing pneumonitis limited the lesion from the uninvolved lung. The arteries were plugged by organized and canalized thrombi, and the pleural surface was covered by a membrane of fibrin and numerous neutrophils. Large bacterial clumps, containing cocci and bacilli, were found within the areas of necrosis and suppuration and in the pleural membrane. Similar bacterial clumps were seen in the mural thrombus in the right ventricle, but since there was no sign of inflammation of the underlying wall, it was believed that this represented agonal or postmortem bacterial invasion and proliferation.

The final anatomic diagnosis was: Acute encapsulated fibrinopurulent pleuritis, pulmonary infarction of right upper lobe with necrosis, cavitation, and suppurative pneumonitis, pulmonary arterial embolism and thrombosis, hypertrophy and dilatation of the heart, atherosclerosis of the coronary arteries and organized thrombosis of the anterior descending branch of the left coronary artery, organized infarct of the anterior left ventricular wall, organizing mural thrombi of the right and left ventricles, chronic passive congestion of the liver, arteriolar nephrosclerosis.

Summary of Case 2. A 45-year-old arteriosclerotic cardiac suffered a coronary thrombosis accompanied by a myocardial infarct and mural thrombosis of both ventricles. Several episodes suggesting pulmonary infarction were observed, and the last of these was followed by extensive necrosis, cavitation and suppuration of the infarct, with pleural extension and encapsulated suppurative pleuritis.

CASE 3.—G. B., a 49-year-old male, first came under our observation on October 18, 1933, at which time he entered the hospital because of cough and blood-streaked expectoration. He acquired a chancre in 1926, and had experienced dyspnea and radiating precordial pain on exertion since 1929. These symptoms had become more marked in the 2 weeks preceding admission, and a bloody expectoration appeared. Physical examination revealed signs of enlargement of the heart and aortic insufficiency. There were no signs of congestive heart failure. There were auscultatory and Roentgen-ray signs of pulmonary consolidation corresponding to the right middle lobe, and later a friction rub appeared. There was fever for 3 days, the sputum showed unclassified pneumococci and the blood culture was negative. The pulmonary signs cleared and convalescence was interrupted

by two brief severe attacks of precordial pain. He was discharged on November 3, 1933. The Wassermann reaction was negative.

He reentered on February 20, 1935, for the consideration of hemorrhoidectomy. Signs of congestive heart failure were now clearly evident and he was transferred to the medical service without operation. On March 5th pain in the right chest, bloody expectoration and grunting respirations appeared. There were dulness, diminished breath sounds and râles at both bases, and a friction rub was audible in the right axilla. The temperature fluctuated between 102 and 105° and signs of fluid appeared at the right base. Thoracentesis, performed on March 13, yielded 50 cc. of thick greenish-yellow pus. Closed-tube drainage was instituted but exitus occurred the following day.

At necropsy (few hours after death) the right pleural cavity was filled with tenacious yellow-green pus which covered all surfaces, but was particularly thick over the dependent and diaphragmatic surfaces of the right lower lobe. In the right upper lobe was a small recent infarct. The dependent portions of the right lower lobe presented a firm, dry, dark-red appearance and within this hemorrhagic area were small irregular grayish-white zones. The arteries leading to the dependent portion of the right lower lobe were plugged by thrombi. The postmortem lung-culture yielded hemolytic streptococci and unclassified pneumococci.

Microscopic sections through the right lower lobe revealed a varying picture. There were well demarcated areas of hemorrhagic infarction partly surrounded by zones of neutrophilic alveolar exudation with necrosis of alveolar walls, abscess formation and extension to the pleura. Numerous cocci, appearing generally as paired or isolated organisms, less commonly in chains, were demonstrable in these regions in the Gram-Weigert preparations. Elsewhere were zones of acellular, eosinophilic, amorphous débris encircled by a region of suppurative pneumonitis.

The final anatomic diagnosis was: Acute fibrinopurulent pleuritis, right, hemorrhagic infarction and suppurative pneumonitis of right lower lobe, pulmonary arterial thrombosis or embolization, hypertrophy and dilatation of the heart, syphilitic aortitis with fusiform aneurysm of the ascending aorta, coronary ostial stenosis and aortic insufficiency, thrombosis of the right auricular appendage, chronic passive congestion of the liver.

Summary of Case 3. A 49-year-old white male, with syphilitic heart disease, aortic insufficiency and coronary ostial stenosis, developed signs of hemorrhagic infarction of the lung while in congestive heart failure. The initial thoracentesis, performed 8 days following the appearance of symptoms of pulmonary infarction, yielded frank pus. Necropsy revealed areas of suppurative pneumonitis surrounding the infarct and postmortem lung culture disclosed the presence of pneumococci and hemolytic streptococci.

CASE 4.—J. M., a 41-year-old chronic alcoholic, who had been repeatedly admitted for acute alcoholism, entered the hospital on January 10, 1936, in a condition of acute alcoholic intoxication. The heart did not appear enlarged on physical examination, and the blood pressure was 150/108. There were no signs of congestive heart failure, but edema of the legs and neurologic evidence of peripheral neuritis were noted.

While ambulatory on the wards, on January 20, 1936, he suddenly exhibited paroxysmal dyspnea, orthopnea, cyanosis and evidence of congestive heart failure. The blood pressure was 110/90, a gallop was audible

at the apex, the rate was 130, and the standard and precordial lead electrocardiograms suggested myocardial infarction involving the anterior wall of the left ventricle.

On January 25, 1936, bloody expectoration appeared and signs of fluid at the right base, and consolidation at the left base, were elicited. Thoracentesis of the right chest on January 30 yielded 700 cc. of clear yellow fluid. Thoracentesis was repeated on the right, and also performed on the left chest, on February 11, and 175 cc. of turbid yellow fluid were obtained from the former, and 1400 cc. of turbid brownish fluid from the latter. The cells in the pleural fluid were mostly lymphocytes (88% and 78% respectively). Both chests were retapped on March 6 with similar results. The patient continued in a downhill course showing progressively severe failure. Physical and Roentgen-ray evidence (Fig. 3) of bilateral effusion persisted. On April 16 thoracentesis of the left chest yielded 700 cc. of grayish fluid; although neutrophils predominated in the smear of the sediment, no organisms were demonstrable by Gram staining. The right chest was retapped on April 17 and 300 cc. of bloody fluid obtained, and again tapped on April 21, at which time a similar fluid was obtained, yielding *Streptococcus viridans* on culture. The patient's condition grew rapidly worse and death occurred on May 17, 1936.

At necropsy (2 hours after death) about 500 cc. of purulent fluid were found in the right pleural sac, and about 850 cc. of similar fluid were encapsulated at the base of the left pleural cavity. The visceral and parietal pleura measured 5 mm. or more in thickness and consisted of dense fibrous tissue with a superficial layer of shaggy fibrinous material. Projecting into the encapsulated empyema cavity at the left base, was a large, well circumscribed infarct, which appeared as a friable, softened, necrotic, reddish-gray mass. A similar smaller infarct, with its base at the diaphragmatic pleura, was encountered in the anteromedial portion of the right lower lobe. The pulmonary arteries at the hilus of the left lung contained organizing thrombi, and more distally, the vessels were completely occluded by partially and completely organized thrombi. The large arteries in the right lower lobe were similarly occluded but the vessels were patent at the hilus.

Microscopic sections of the infarcts showed well demarcated zones of infarction from which most of the blood had already been resorbed, leaving necrotic remnants of alveolar walls. The peripheral rim of necrotic lung was densely infiltrated by neutrophils and abscesses were frequently encountered. A few isolated cocci were demonstrated in these regions by the Gram-Weigert technique. The infarcts were circumscribed from the uninvolved lung by a broad zone of granulation tissue, and the arteries were occluded by organized thrombi. The pleura was markedly thickened and covered by a layer of fibrin and neutrophils.

The final anatomic diagnosis was: Chronic bilateral fibrinopurulent pleuritis, multiple organizing and softened pulmonary infarcts with suppurative pneumonitis, multiple organizing pulmonary arterial thrombi or emboli, hypertrophy and dilatation of the heart, coronary atherosclerosis, patchy fibrosis of apex of the left ventricle with superimposed organizing mural intraventricular thrombi, chronic passive congestion of the liver, multiple infarcts of the kidneys, ascites.

Summary of Case 4. A 41-year-old chronic alcoholic, with an enlarged heart and coronary atherosclerosis, suddenly developed signs of myocardial infarction and congestive heart failure. This was followed by signs and symptoms of pulmonary infarction at both bases, accompanied by an initially serous effusion. Thoracentesis

was repeatedly necessary, and the pleural fluid assumed a purulent character almost 3 months following the pulmonary infarction. *Streptococcus viridans* was obtained on culture of the chest fluid on one occasion. Necropsy revealed old necrotic infarcts surrounded by zones of suppurative pneumonitis and undergoing organization.

Discussion. The gross and microscopic findings in all 4 cases support the view that secondary infection of the pulmonary infarcts led to suppurative pneumonitis and pleuritis. In 2 cases (2 and 3) the possibility of contamination of the pleural space by thoracentesis may be excluded. In Case 3 the initial tap was purulent, and in Case 2, although the initial tap was sero-sanguinous, necropsy performed the following day disclosed a purulent effusion, which had evaded thoracentesis because of encapsulation at the base, in addition to the serosanguinous effusion. The suppuration of the infarcts and of the lung immediately surrounding the latter, in all 4 cases, further fortifies the belief that the pleura became infected by microorganisms invading from the lung and not introduced during thoracentesis.

The emboli and thrombi responsible for the infarcts were of bland character, and the former were derived from mural thrombi in the right auricular appendage and ventricle in Case 1, in the right ventricle in Case 2, and in the right auricular appendage in Case 3. The source of the emboli was not demonstrated in Case 4, but the peripheral venous system was not examined.

The microorganisms which caused the pulmonary and pleural suppuration varied in type. *Strep. hemolyticus* and diphtheroid bacilli were cultured from the pleural fluid in Case 1, *Strep. viridans* from the pleural fluid in Case 4, and hemolytic streptococcus and pneumococcus were demonstrated by postmortem culture of the lung in Case 3. The abundance of the bacterial colonies in the sections of the lung and pleura in Case 2, and their presence in the mural thrombus of the right ventricle, are probably attributable to postmortem bacterial proliferation and invasion, occurring in the 6-day interval between death and necropsy.

The source of the microorganisms and their route of dissemination to the pulmonary infarcts have not been ascertained. It is probable that the bacteria were derived from the respiratory passages. Ceelen¹ has expressed the belief that bronchogenic dissemination of microorganisms may bring about suppuration of a pulmonary infarct. Holman and Mathes² have experimentally produced abscess formation in bland pulmonary infarcts by intravenous injections of microorganisms. In the cases herein reported, however, bronchogenic infection appears the more likely route. Blood cultures taken in 2 of the 4 cases (1 and 3) were sterile. Bronchogenic infection of the lungs is a common occurrence in congestive heart failure and frequently brings about secondary pneumonia. It is

probable that the infarcted lung offers an unusually favorable soil for the propagation of bacteria, and that in the presence of ischemic necrosis, extensive suppuration rapidly ensues. In only one subject (Case 3) did the suppurative pneumonitis complicate recent pulmonary infarction, and in this instance the initial tap yielded purulent fluid. In the other cases the infarcts were older, and had undergone softening (Cases 1 and 4), and cavitation (Case 2), and the clinical signs suggest that the infarcts antedated the suppurative pleuritis by a period varying from several weeks (Case 2), to 2 and 3 months (Cases 1 and 4). In the interval between infarction and empyema sterile pleural effusions were encountered.

Clinical experience with these cases reflects the confusion in differential diagnosis which may arise when the cardiac nature of the initial symptoms is unrecognized or inadequately correlated with the subsequent pulmonary phenomena. The latter may simulate pulmonary neoplasm, pneumococcus or streptococcus pneumonia with postpneumonic empyema, or cavernous pulmonary tuberculosis with pleural effusion.

Although empyema was recognized clinically in 3 of the cases, the coexistence of severe congestive heart failure discouraged surgical interference. That such cases may be occasionally amenable to surgical drainage is illustrated by Touroff's⁶ experience, in which recovery followed thoracotomy for intrapulmonary empyema associated with pulmonary infarction in a rheumatic cardiac with congestive heart failure.*

Summary. In the foregoing report are presented the clinical and necropsy findings of 4 cases of congestive heart failure, in whom suppurative pleuritis complicated pulmonary infarction. The evidence is discussed which indicates that bland pulmonary infarcts may spontaneously undergo secondary infection which leads to empyema by penetration of the microorganisms to the pleura.

* Recently, one of us (C. C.) had the privilege of observing and treating a case of suppurative pleuritis following pulmonary infarction secondary to coronary thrombosis, at the Lenox Hill Hospital. Surgical drainage was performed by Dr. Carl Eggers and the patient made an uneventful recovery. However, several months later he returned to the hospital in congestive heart failure. Bed rest and digitalis partially restored his cardiac reserve.

REFERENCES.

- (1.) Ceelen, W.: Die Kreislaufstörungen der Lunge, *Handb. d. spez. patholog. Anat. u. Histol.*, Henke, F. and Lubarsch, O., Berlin, Julius Springer, 3, Pt. 3, 1931.
- (2.) Holman, E., and Mathes, M. E.: *Arch. Surg.*, 19, 1246, 1929. (3.) Juergensen, T.: Hypostatische Vorgänge in der Lunge, *Handb. d. Spec. Pathol. u. Therap.*, H. V. Ziemssen, Leipzig, F. C. W. Vogel, 5, 248, 1874. (4.) Lord, F. T.: Diseases of the Bronchi, Lungs and Pleura, Philadelphia, Lea & Febiger, p. 335, 1915. (5.) Staehelin, R.: Die Erkrankungen der Trachea, der Bronchien, der Lungen und der Pleuren, *Handb. d. Inn. Med.*, Berlin, Julius Springer, 2, 1142, 1930. (6.) Touroff, A. S.: *Surg., Gynec. and Obstet.*, 57, 156, 1933.

OBSERVATIONS ON THE ETIOLOGIC RELATIONSHIP OF ACHYLIA GASTRICA TO PERNICIOUS ANEMIA.

VI. THE SITE OF THE INTERACTION OF FOOD (EXTRINSIC) AND GASTRIC (INTRINSIC) FACTORS; FAILURE OF *in Vitro* INCUBATION TO PRODUCE A THERMOSTABLE HEMATO- POIETIC PRINCIPLE.*

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It is well known that the oral or parenteral administration of suitable extracts of mammalian liver leads to increased blood production and clinical improvement in patients with pernicious anemia. The oral administration of normal human gastric juice (intrinsic factor) together with beef muscle^{2,3,4a} or certain other substances^{1,12} (extrinsic factor) produces identical effects in such patients. The livers of persons who have died of pernicious anemia before treatment could be applied are lacking in the active principle present in normal human and animal livers.¹¹ These facts have led to the assumption that the effective principle in the liver of the normal person is in some way formed from the interaction of food and gastric factors. The problem as to how and where in the body such a transformation occurs remains, however, quite unsolved.

Convincing evidence is lacking for any specific enzyme action of normal human gastric juice *in vitro* on the nitrogenous components of sources of extrinsic factor.⁶⁻⁸ Indeed, it has been shown that normal human gastric juice freed by adsorption methods of both pepsin and rennin still contains intrinsic factor.^{4b,9} Klein and Wilkinson's¹⁰ claim that they have demonstrated the *in vitro* synthesis of the active principle of liver in incubated mixtures of preparations of hog's gastric mucosa and beef muscle cannot be accepted,

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because the mixtures were not subjected to the relatively high temperatures, 80° to 120° C., known to be without significant destructive effect on relatively crude liver fractions. The fact that the administration of beef muscle and gastric juice *separately* at an interval of 6 hours results in increased blood production² eliminates the necessity of hypothecating an *in vitro* phase for the production of the activity of incubated mixtures. Although the respective administration of beef muscle and gastric juice separated by an interval of 12 hours or more leads to negative effects on blood production,² this fact in no way defines the site of effective interaction between beef muscle and gastric juice when given coincidentally. Indeed, the fact that neutral mixtures of beef muscle and gastric juice are effective when administered to the achyllic pernicious anemia patient implies that a neutral reaction is suitable for the development of their activity. Therefore, so far as the reaction is concerned a suitable environment might be found as well after absorption within the body as before leaving the alimentary tract.

Obviously, more information concerning the site and the conditions essential for interaction of the extrinsic and intrinsic factors is desirable. The purpose of this communication, therefore, is to present evidence that an essential stage in the development of a hematopoietic principle takes place, possibly *in vitro*, but certainly within the alimentary tract rather than parenterally. The active principle of liver, however, is not formed *in vitro* by the interaction of food and gastric factors. The conditions of the observations suggest that if an enzyme is involved in the interaction between extrinsic and intrinsic factors, it is not active in an environment more acid than pH 2.5.

Methods. The 9 patients on whom the present observations were made all had typical Addisonian pernicious anemia and responded eventually and characteristically to the administration of mixtures of beef muscle and gastric juice or to the administration of liver extract. The methods of dietary control and of red blood cell and reticulocyte counting, as well as the interpretation of effects on blood production, have been fully described elsewhere.^{3,4a} The gastric juice was secreted daily by normal fasting individuals following the intramuscular injection of 0.5 mg. of histamine. It was kept in the ice box without neutralization until required for use. After incubation the semi-liquid mixture of beef muscle and gastric juice was given daily to the patient by stomach tube.

Observations. *Mixtures of beef muscle and gastric juice administered at pH 1.8 to 2.5 are ineffective.* The purpose of the following observations was to determine whether a change in the reaction of the upper alimentary tract would affect the blood-forming activity of mixtures of beef muscle and gastric juice. To effect this, use was made of the natural buffering properties of incubated mixtures of beef muscle and gastric juice. By means of a stomach tube either acid or neutral mixtures were administered.

The contents of the stomach of a normal man was recovered 1

hour after the ingestion of a meal of 300 gm. of beef muscle. It was then liquefied by subsequent incubation at 37.5°C . at pH 2.5—half of it for 6, and half of it for 30 hours. To Case 2 this material was given daily at pH 2.5 during a first period. No significant effect on blood production appeared, as is shown in the table. In the immediately following second period, the procedure was identical *except that the incubated gastric contents was brought to pH 5* with a saturated solution of sodium hydroxide immediately before administration to the patient. A positive effect on blood production appeared. To Case 71 was given daily during a first period a mixture of 200 gm. of beef muscle, 150 cc. of gastric juice and 5 gm. of pepsin, incubated for 6 hours at pH 1.8 and administered at that reaction. No significant effect on blood production appeared. In the immediately succeeding second period, the daily procedure was the same *except that the material was brought to pH 7* by the addition of a saturated solution of sodium hydroxide immediately before administration to the patient. A positive effect on blood production appeared, as is shown in the table.

Whether the failure of the acid digest to cause increased blood production was due to the destruction of the extrinsic or the intrinsic factors before effective interaction could occur or whether it was due to such acidity that interaction could not take place was the basis of further analysis. That the administration of such an acid digest of beef muscle may influence for some time the reaction of the upper intestinal contents is probable, since concentrated sodium hydroxide equivalent to 450 cc. of 0.1 normal sodium hydroxide solution was required in order to bring the mixture from pH 1.8 to neutrality. Therefore, although incubation of a mixture of beef muscle and gastric juice at pH 1.8 or 2.5 for 6 hours did not abolish its activity provided it was brought to pH 5 or 7 before being given to the patient, if the mixture was not so neutralized it could be argued that after administration to the patient continued *in vivo* incubation of the acid mixture was responsible for failure through subsequent destruction of the intrinsic factor.² In order to test this possibility, 200 gm. of beef muscle were incubated with 5 gm. of pepsin and 150 cc. of gastric juice for 12 hours at pH 1.8. This material was then brought to pH 7 and given to Case 72 daily. A significant effect on blood production resulted (Table 1). It therefore appears probable that the negative effect of administration of incubated mixtures of beef muscle and gastric juice at an acid reaction in Cases 2 and 71 was not due to a prolongation of any destructive action of the acid medium on the extrinsic or intrinsic factors after administration to the patient.

Therefore, unless in some way the acidity of the mixture merely prevented the absorption of one or more of the active constituents of the digests, it is reasonable to suppose that the administration of the mixture of beef muscle and gastric juice at an acid reaction

inhibited the essential interaction between these substances. The fact that a change in the pH of the mixture would not significantly affect the pH of the parenteral tissues certainly suggests that with neutral digests an interaction takes place, possibly *in vitro*, but at least within the alimentary tract rather than parenterally. That this interaction is carried out by an enzyme in the gastric juice is possible, though by absorption with Hammarsten casein solution we^{4b} (see also second period of Case 78 in the table), as well as Helmer, Fouts and Zerfas,⁹ have prepared filtrates of normal human gastric juice containing active intrinsic factor but apparently without pepsin or rennin-like action. Moreover, the *in vitro* observations of Griffiths⁷ and of Helmer and Emerson^{6,8} do not appear to have demonstrated a specific enzyme acting on sources of extrinsic factor. Nevertheless, if the specific effect on extrinsic factor is produced by an enzyme it can now be stated as probable that its activity occurs in the vicinity of the neutral point and is slight, if any, at reactions of pH 2.5 or less.

Temperatures without significant destructive effect on aqueous solutions of an unpurified liver extract abolish the activity of mixtures of beef muscle and gastric juice after incubation for 2 hours at pH 7. In the preparation of the liver fraction "G" of Cohn, Minot and their associates,⁵ temperatures of 80° C. are employed. Moreover, the activity of neutral aqueous solutions of this fraction successfully resists boiling or autoclaving as a means of sterilization. Thus in the table are shown the positive effects on blood production in a patient with pernicious anemia, Case 73, who was given daily by intramuscular injection a neutral aqueous solution of liver fraction "G" which had previously been autoclaved for 3 hours at 120° C. The daily dose was 2 cc., containing material derived from 10 gm. of liver. It is thus clear that in order to establish the presence of such a thermostable substance in a mixture of beef muscle and gastric juice the activity of the mixture should withstand autoclaving and certainly lower temperatures.

The material given daily during the first period of Case 74 was prepared as follows. Two hundred grams of beef muscle, 5 gm. of pepsin and 100 cc. of water were incubated at 37.5° C. at pH 2.5 to 3.5 for 6 hours. Then 75 cc. of gastric juice were added and the mixture was incubated at 37.5° C. at pH 7 for 2 hours. Thereafter hydrochloric acid was added until a pH of 2.5 to 3.5 was attained and the mixture incubated for 72 hours at 40° C. The material so prepared in advance was finally adjusted to pH 5 and given daily with no significant effect on blood production. In an immediately succeeding second period the procedure was identical *except that the material was not incubated for 72 hours at 40° C.* A positive effect on blood production resulted.

Temperatures without significant destructive effect on aqueous solutions of liver extract abolish the activity of mixtures of beef muscle with

normal human duodenal contents or with hog duodenal and small intestinal mucosa after incubation for 2 hours at pH 7. Since the *in vitro* incubation of beef muscle and gastric juice was not shown to produce a substance resembling in thermostability the active principle of liver, the question arose as to whether such a substance would be formed if a further *in vitro* imitation of normal digestive processes was attempted by the addition of normal human duodenal contents or of hog duodenal and small intestinal mucosa.

Accordingly, during the first period of Case 75, the following procedure was carried out. One hundred grams of beef muscle, 4 gm. of pepsin and 50 cc. of water were incubated at 37.5° C. for 12 hours at pH 2.5 to 3.5. This liquid material was then introduced into the stomach of a normal fasting subject into whose duodenum had previously been passed a Levin catheter. To 200 cc. of the duodenal contents recovered, which contained bile and partially digested beef muscle, were added 200 gm. of beef muscle and 4 gm. of pepsin. The mixture was then incubated for 1 hour at pH 2.5 to 3.5. Then 125 cc. more of the duodenal contents were added and the mixture incubated at pH 7 for 2 hours. The material was then boiled for 5 minutes, cooled, and immediately given to the patient, Case 75, daily by stomach tube during a first period. No significant effect on blood production resulted. In an immediately subsequent second period, however, during which the procedure was the same *except that the final mixture was not boiled for 5 minutes*, a positive result appeared, as is shown in the table.

During the first period of Case 76, the following procedure was carried out daily. Two hundred grams of beef muscle, 100 cc. of water and 5 gm. of pepsin were incubated at 37.5° C. for 2 hours at pH 2.5 to 3.5. Seventy-five cubic centimeter of gastric juice were then added, the mixture was brought to pH 7 and incubated for 1 hour. Then 100 gm. of freshly prepared mucosa, stripped from the duodenum and upper small intestine of hogs, were added and the mixture was incubated for 1 hour at pH 7, then heated to from 70° to 80° C. for 30 minutes. Immediately after cooling, the material was given daily to Case 76 without significant effect on blood production, as is shown in the table. During an immediately succeeding period the same procedure was carried out daily *except that the final mixture was not heated to 70° to 80° C. for 30 minutes*. A positive result appeared (Table 1).

It is therefore evident that the incubation of the mixtures of beef muscle with normal human gastric juice and subsequently with normal human duodenal contents or with the mucosa of the duodenum and small intestine of the hog does not produce *in vitro* a substance which is resistant to heat, as is the active principle of whole liver or of relatively unpurified liver extract.

That the destructive effect of temperature on the mixture given these patients was not on the extrinsic factor in the beef muscle is

	First Periods.	Daily Administration of Various Sub-
CASE 2.	CASE 71.	CASE 72.

CASE 2.	CASE 71.	CASE 72.	CASE 73.	CASE 74.	CASE 75.	CASE 76.	CASE 77.	CASE 78.
Gastric contents containing 200 gm. beef muscle incubated 6-30 hours at pH 2.5.	Beef muscle 200 gm., pepsin .5 gm., gastric juice 150 cc. incubated 6 hours at pH 1.8. Given at pH 7.	Beef muscle 200 gm., pepsin .5 gm., gastric juice 150 cc. incubated 12 hours at pH 1.8. Given at pH 7.	Solution liver extract — Lilly (N.R.), auto-claved 3 hours at 120° C. 2 cc. from 10 gm. of liver intramuscularly.	Beef muscle 200 gm., pepsin .5 gm., gastric juice 75 cc. incubated 2 hours at pH 7, then incubated for 72 hours at pH 2.5-3.5. Given at pH 5.	Beef muscle and duodenal contents incubated 2 hours at pH 7, then boiled 5 min. (See text for details.)	Beef muscle and hog duodenal and small intestinal mucosa incubated 2 hours at pH 7, then 70°-80° C. for 30 min. (See text for details.)	Beef muscle 200 gm., pepsin .5 gm., incubated 18 hours at pH 2.5-3.5, then boiled 5 min. Then added to gastric juice 75 cc. at pH 7.	Beef muscle 200 gm., pepsin .5 gm., digest added to gastric juice 75 cc. previously incubated at 40° C. for 72 hours at pH 1.5. Given at pH 5.
Days of treatment.								
0	R.B.C. (mils.). Retics. (%)	R.B.C. (mils.). Retics. (%)	R.B.C. (mils.). Retics. (%)	R.B.C. (mils.). Retics. (%)	R.B.C. (mils.). Retics. (%)	R.B.C. (mils.). Retics. (%)	R.B.C. (mils.). Retics. (%)	R.B.C. (mils.). Retics. (%)
2	1.03 3.8	1.60 1.6	2.23 0.8	2.40 0.0	2.24 0.2	1.98 0.2	1.44 0.8	1.25 1.2
4	0.75 2.5	1.44 1.0	2.25 1.2	2.14 0.4	2.20 0.2	1.19 0.4	1.33 0.6	1.53 0.4
6	0.75 4.6	2.2 1.73	2.06 0.8	2.42 0.4	2.25 0.1	1.37 0.4	1.46 0.4	1.21 0.4
8	0.69 3.2	1.58 1.0	2.35 2.52	2.52 0.8	2.00 0.2	1.23 0.1	1.43 3.2	1.22 0.8
10	0.84 3.2	1.55 0.8	2.67 4.8	2.65 0.6	1.94 0.4	1.15 0.1	1.56 7.4	1.01 0.8
12								
14			2.73	1.6			1.62	1.6

Second Periods.—Daily Administration of Various Substances as Indicated Below.

Same as above except given at pH 5.	Same as above except not incubated 72 hours at pH 7.	Same as above except not heated 70°-80° C. for 30 min.	Same as above except gastric juice filtrate used after iso-electric precipitation with casein, then shaken with basic magnesium carbonate.
R.B.C. (mils.). Retics. (%)	R.B.C. (mils.). Retics. (%)	R.B.C. (mils.). Retics. (%)	R.B.C. (mils.). Retics. (%)
0.65 3.4	2.87 0.2	1.82 0.2	1.09 1.0
0.80 9.8	2.77 3.2	2.10 3.8	1.28 1.6
0.86 6.6	2.92 2.6	0.85 0.1	1.22 3.2
0.89 16.0	2.85 6.8	2.6 0.93	1.35 8.4
1.10 15.0	3.09 7.0	12.5 7.2	1.42 19.6
1.44 7.4	2.6 2.6	5.4 0.8	1.86 12.4
1.48 5.1			1.97 2.8

clear. Mixtures of gastric juice with a 48-hour peptic digest of beef muscle previously boiled for 5 minutes (Case 77, Table 1), with autoclaved, autolyzed yeast (Vegex)¹² or with hog stomach mucosa which has been boiled for 2 hours,² are hematopoietically effective. It is, however, possible that the destructive effect of temperature on mixtures of beef muscle and gastric juice may have been due simply to destruction of the intrinsic factor. We have shown elsewhere that the activity of the intrinsic factor of gastric juice is significantly diminished by incubation at 37.5° C. for 2 hours at pH 1.5² and is completely destroyed by incubation at 40° C. for 72 hours at pH 1.5^{4b} (first period of Case 78, Table 1), by a temperature of 70° to 80° C. for 30 minutes² or by boiling for 5 minutes.¹ Nevertheless, opportunity for the development of a thermostable substance from the already liquefied beef muscle during the 2-hour incubation at neutrality, especially in the presence of both normal gastric and duodenal contents, would appear to have been provided.

Klein and Wilkinson¹⁰ claim to have demonstrated the *in vitro* synthesis of the active principle of liver in an incubated mixture of a preparation of hog stomach with beef muscle. They found that the activity in pernicious anemia of "haemopoietin," a preparation derived from hog stomach, was destroyed by exposure to a temperature of 60° to 65° C. for 30 minutes. After incubation with beef muscle at 37° C. for 2 or 6 hours at pH 5.7, however, the activity of the mixture was not destroyed by a temperature of 60° to 65° C. for 30 minutes. On the contrary, our observations in the first periods of Cases 74, 75 and 76 show that subsequent incubation at 37.5° C. for 72 hours, boiling for 5 minutes or heating to 70° to 80° C. for 30 minutes destroyed the blood-forming activity of beef muscle after 2-hour incubation at 37.5° C. at pH 7 with gastric juice, duodenal contents and small intestinal mucosa, as shown in the second periods. Since such temperatures are not destructive of the activity of dilute solutions of the fraction "G" of Cohn, Minot and their associates, it is clear that without other means of identification it cannot be assumed that this relatively thermostable substance was formed *in vitro*. Since Klein and Wilkinson did not test the destructive effect of temperatures above 60° to 65° C., their evidence that the thermostable active principle of liver extract was synthesized *in vitro* cannot be accepted. Indeed, the rather slight differences in thermostability observed may have been entirely due to the protective effect of the beef muscle on the preparation of hog stomach mucosa. It cannot be denied, however, that some new substance of slightly greater thermostability than the hog stomach preparation may have been synthesized in their experiments.

Conclusions. 1. Administration of mixtures of beef muscle and normal human gastric juice at pH 1.8 or 2.5 does not lead to the

increased blood production in pernicious anemia which occurs when mixtures of these substances are administered at pH 5 or pH 7.

2. Since the negative results from administration of such acid mixtures were shown not to be due to destruction of intrinsic factor, it is probable that the acid environment was unsuitable for an essential interaction between beef muscle and gastric juice.

3. Since the inhibitory effect of the acid environment would be largely confined to the alimentary tract, it is inferred that normally the essential interaction between extrinsic and intrinsic factors takes place enterally rather than parenterally.

4. The synthesis of a substance resembling in thermostability the active principle of crude liver extracts was, however, not effected *in vitro* by 2-hour incubation at pH 7 of beef muscle with (a) normal human gastric juice or (b) thereafter with normal human duodenal contents or (c) with normal human gastric juice and thereafter with hog duodenal and small intestinal mucosa.

5. Despite lack of present evidence for specific *in vitro* effects, the possibility remains that the gastric intrinsic factor is an enzyme active near pH 7, but not at pH values less than 2.5. If active under *in vitro* conditions, its function would appear to be the development of some precursor of the thermostable active principle of liver extract.

REFERENCES.

- (1.) Castle, W. B.: Science, 82, 159, 1935. (2.) Castle, W. B., and Ham, T. H.: J. Am. Med. Assn., 107, 1456, 1936. (3.) Castle, W. B., and Townsend, W. C.: AM. J. MED. SCI., 178, 764, 1929. (4.) Castle, W. B., Townsend, W. C., and Heath, C. W.: (a) Ibid., 180, 305, 1930; (b) J. Clin. Invest., 9, 2, 1930. (5.) Cohn, E. J., Minot, G. R., Alles, G. A., and Salter, W. T.: J. Biol. Chem., 77, 325, 1928. (6.) Emerson, C. P., Jr., and Helmer, O. M.: Am. J. Digest. Dis. and Nutrit., 3, 753, 1936-37. (7.) Griffiths, W. J.: Biochem. J., 28, 671, 1934. (8.) Helmer, O. M., and Emerson, C. P., Jr.: Am. J. Digest. Dis. and Nutrit., 3, 906, 1936-37. (9.) Helmer, O. M., Fouts, P. J., and Zerfas, L. G.: AM. J. MED. SCI., 188, 184, 1934. (10.) Klein, L., and Wilkinson, J. F.: Biochem. J., 28, 1684, 1934. (11.) Richter, O., Ivy, A. C., and Kim, M. S.: Proc. Soc. Exp. Biol. and Med., 29, 1093, 1932. (12.) Strauss, M. B., and Castle, W. B.: New England J. Med., 207, 55, 1932.

THE ETIOLOGY AND TREATMENT OF IDIOPATHIC HYPOCHROMIC ANEMIA.*

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DURING iron balance experiments on patients with hypochromic anemia, certain observations were made regarding the pathogenesis of that form which is commonly known as "idiopathic hypochromic

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anemia." Though much has been written on this disease, and many hypotheses advanced to explain its etiology,^{3,26} little in the way of absolute proof to support these assumptions has been forthcoming. The clinical and hematological features have been sufficiently emphasized so that a detailed discussion of these is unnecessary. In this anemia, occurring almost exclusively in middle-aged women usually associated with a deficient gastric secretion, the erythrocytes are small and pale. Dysphagia, koilonychia, paresthesia without evidence of cord degeneration, and glossitis are of frequent occurrence, together with the usual symptoms of a severe anemia. A history of excessive blood loss is seldom obtained, so that the actual etiology of the anemia has been in doubt.

There are many similarities between this anemia and that of chronic hemorrhage. Insofar as the blood smear is concerned, there is nothing in the morphological changes of the erythrocytes on which to base a differentiation of the two conditions, and there are no essential differences in the color, volume, or saturation indices. Koilonychia, which has been frequently emphasized as a feature of the idiopathic form, may be present in chronic hemorrhagic anemia as is evidenced by the following case:

Case Abstract. A white male, aged 47, began to have periodic epigastric distress 15 years before admission to this hospital. The distress appeared intermittently and there were several episodes of severe hemorrhage. A diagnosis of duodenal ulcer was made, and a gastro-enterostomy was performed. He felt quite well until 5 years prior to his admission when he had a hemorrhage so severe that he was confined to bed for several months. He had lost no gross blood since that time, but had continued to be weak and pale. These symptoms increased, and at the time of admission he presented the usual manifestations of severe anemia.

Chemical examination of the stools revealed that he continually passed small amount of occult blood. There were 1.5 gm. of hemoglobin per 100 cc. of blood, 1,100,000 erythrocytes per cm., and an hematocrit of 7%. The finger nails were thin, brittle, and spoon shaped, and the patient had noted the onset of these features 2 years previously. Under medical management, the bleeding became less severe but did not entirely cease. With the administration of iron and ammonium citrates, 3 gm. per day, the hemoglobin increased to 9.2 gm., and the erythrocyte count to 4,910,000, and the finger nails became normal.

Although dysphagia, glossitis, and atrophy of the tongue are frequent in idiopathic hypochromic anemia, we have never encountered these features in a case of chronic hemorrhagic anemia unassociated with deficient gastric secretion. These manifestations, together with the achlorhydria, are the only characteristics that suffice for differentiation of the two conditions aside from the history of chronic hemorrhage. Dysphagia was present in 6 of the 11 cases of idiopathic hypochromic anemia on whom iron balance determinations were made, and in every instance it disappeared completely when the blood hemoglobin returned to normal with no dilatation of the esophagus except that incident to a single esophagos-

copy. We do not believe, however, that the anemia *per se* is responsible for the esophageal spasm inasmuch as it did not occur in any of the cases with uncomplicated chronic hemorrhagic anemia.

Menstrual Blood Loss. The fact that idiopathic hypochromic anemia is almost exclusively confined to women, and especially to women of the child bearing age, has naturally led to the assumption that the periodic menstrual blood loss is one factor in its etiology. On the other hand, menorrhagia has been considered by some to be a result or a symptom of the anemia rather than the cause. We have questioned our patients carefully in regard to their menstrual blood loss and none was included in the idiopathic group who acknowledged excessive menstruation. All those with such a history were classified as chronic hemorrhagic anemia, regardless of the gastric acidity or other findings.

During the iron balance studies,^{1b,11,12} it was necessary to ascertain the amount of iron and hemoglobin lost during menstruation in several instances, but in attempting to evaluate these results a review of the literature gave us no definite information as to what constituted the normal menstrual blood loss. We, therefore, made such determinations in 100 non-anemic, normal women, who, as far as they could judge, had a normal menstrual flow. It was found^{1a} that the hemoglobin lost per menstrual period varied from 0.68 gm. to 23.57 gm. which represented from 6.6 to 178.7 cc. of the patient's blood. The average loss for the 100 subjects was 50.6 cc. of blood, and 50% of the women lost between 23 and 68 cc. In general, there was some correlation between the amount of hemoglobin lost, the duration of the menstrual flow, and the number of napkins used; but in certain instances there was a marked discrepancy. It is obvious that one cannot depend entirely on the patient's statement as to the normality of the menstrual flow, as she has no standard on which to base a comparison. When these menstrual losses were considered in terms of iron, it was found that a daily iron retention of from 0.08 mg. to 3.29 mg. would be necessary to replace that lost through menstruation alone. Although none of these women were anemic, it is apparent that even a supposedly normal menstrual flow may constitute a serious drain on the iron stores of the body, and undoubtedly will lead to an anemia when associated with certain other abnormalities.

The menstrual blood loss was determined in 11 cases of idiopathic hypochromic anemia and in every case the individual had considered this loss to be normal. It will be noted (Table 1) that the hemoglobin lost per period varied from 3.18 gm. to 54.36 gm., and that in only 3 cases was the loss within the average range for the 100 normal women. The daily iron retention necessary to counteract the menstrual iron loss varied from 0.38 mg. to 6.5 mg. The results of our iron balance determinations convince us that these higher figures cannot be supplied from the dietary iron alone, since a daily iron

retention of this amount was seldom encountered. The last column in Table 1 gives the actual iron balance for 10 of these patients with idiopathic hypochromic anemia while they were receiving a diet with an iron content of from 10 to 13 mg. per day. It will be noted that in only 2 cases (Cases 2 and 6) was the iron retention sufficient to replace that lost through menstruation. The reason for the development of anemia in these patients is evident from these figures.

Achlorhydria. The frequency with which idiopathic hypochromic anemia is associated with a deficient gastric secretion, as manifest by achlorhydria or hypochlorhydria, has naturally led to the assumption that this feature is either the cause or a prominent contributing factor to the anemia through its influence on the absorption of iron

TABLE 1.—RELATIONSHIP OF MENSTRUAL LOSS TO IRON RETENTION.

Case.	Age.	Blood Hb, gm.	Blood hemat- ocrit, %.	RBC, mills	Menstrual loss.			Daily iron retention necessary to replace menstrual loss, mg	Actual daily iron balance with normal diet, mg.
					Iron, mg.	Hb, gm.	Blood, cc.		
1	34	4 91	27 5	4 91	10 04	3 18	49 20	0 38	-1 37
2	28	6 55	31 0	4 85	10 70	3 19	48 70	0 38	+1 67
3	38	12 41	43 0	5 44	12 24	3 65	29 41	0 43	-7 12
4	34	6 14	31 0	4 48	20 57	7 14	116 28	0 73	+0 20
5	40	6 20	29 0	3 63	47 38	14 14	228 06	1 69	
6	37	6 46	34 0	4 77	49 59	14 80	229 12	1 77	+2 91
7	44	6 26	28 0	4 07	53 42	15 94	254 31	1 91	+0 14
8	25	10 90	36 0	4 52	59 73	17 82	163 48	2 13	-2 62
9	35	4 72	20 5	3 88	145 89	43 54	922 45	5 21	-3 39
10	41	11 80	26 0	4 33	163 00	48 65	412 29	5 82	+1 24
11	40	12 01	38 0	4 75	182 07	54 36	452 42	6 50	-6 66

from the gastro-intestinal tract. Achlorhydria has been demonstrated in patients several years before the development of the anemia,¹⁷ and a hypochromic anemia has also been observed as a sequel to gastrectomy.¹³ Wintrobe²⁶ reports that 17% of the females, and 12.6% of the males had achlorhydria as determined from 11,000 gastric analyses in adults of all ages and Van der Hoof and Davis,²³ in 240 cases of uncomplicated anacidity, found that 69 were males and 171 were females. Only 3 of these males were anemic, whereas 99 of the females had a hemoglobin below 80%. Although it is recognized that iron is better absorbed from an acid than from an alkaline medium, this factor alone does not explain the great preponderance of the disease in females. Further discussions on the relationship of achlorhydria are given by Witts,²⁷ Faber and Grim,⁹ Waugh,²⁴ and by Wintrobe.²⁶

Additional proof that achlorhydria interferes with the absorption of iron is furnished by our iron balance studies. It was found that with a normal iron intake obtained from food alone, the absence of free hydrochloric acid in the gastric juice led to a diminished iron

absorption.^{1c} In 11 cases with achlorhydria, 8 (72.8%) were in a negative iron balance, and the average daily iron balance for the entire group showed a loss of 4.38 mg. In 15 cases with a normal or low gastric acidity only 5 (33 $\frac{1}{3}$ %) were in a negative iron balance, and the average daily iron retention for the group was 1.02 mg. These results show, both by the average daily iron balance, and by the percentage of cases in negative iron balance, that the disturbed gastric secretion diminished the absorption of iron from a normal diet. It was shown, however, that the administration of dilute hydrochloric acid did not increase iron absorption either with a normal dietary iron intake or when large amounts of iron were being administered. This feature suggests that it may not be the lack of hydrochloric acid itself that is at fault but that there may be a deficiency of some unrecognized substance.

These results substantiate the belief that a deficient gastric secretion interferes with the absorption of iron, and that this is an important etiological factor in the production of anemia. Since it does not explain the sex and age incidence of the disease, it is obvious that other factors play a part. When combined with the iron loss in menstruation, the explanation for the anemia as well as the lack of spontaneous improvement becomes evident.

Diet. A dietary deficiency has been suggested as the etiologic factor in many cases of idiopathic hypochromic anemia, especially a diet so low in its iron content that the requirements of the body are not fulfilled. Farrar and Goldhammer¹⁰ found the iron requirement of the body to be considerably below the usually accepted values⁷ and although their patients received from 4.9 to 9.1 mg. of iron per day over long periods of time, they were in positive iron balance and did not develop anemia. Ohlson and Daum¹⁹ found the requirements to be much higher. Our results in 5 patients on a daily iron intake of from 4.14 to 6.74 mg. showed all to be in negative iron balance, but when 4 of these subsequently received from 12.27 to 14.19 mg. of iron per day they were then in a positive balance.^{1c} These results indicate that the requirements are above the figure given by Farrar and Goldhammer, and more nearly agree with Ohlson and Daum. We have never encountered a case of severe idiopathic hypochromic anemia in which we felt that the diet was sufficiently low in its iron content so that this in itself would account for the anemia. We believe that the achlorhydria is of more importance than the actual restriction of the iron intake in the majority of cases.

Pregnancy. It has been noted that the onset of idiopathic hypochromic anemia is frequently associated with pregnancy and in many instances there have been repeated pregnancies with a noticeable weakness persisting between the periods of gestation. Most of these patients with hypochromic anemia of pregnancy have achlorhydria²⁰ and glossitis and this type of anemia has been considered as identical to the idiopathic form. Wintrobe²⁶ found that in 17%

of his patients with idiopathic hypochromic anemia, the onset was quite definitely related to pregnancy. The onset of the anemia in 2 of the 11 patients on whom balance studies were done seemed to be related to frequent and repeated pregnancies.

A diet deficient in iron has been noted in many of the reported cases of hypochromic anemia of pregnancy.²² It has been assumed that the fetal demand for iron so depletes the maternal stores that anemia develops, and Coons⁶ has brought forward more definite proof to substantiate this assumption. She has demonstrated a higher storage of iron in the early months of pregnancy than during the latter part, and has shown that the retention during the late months falls short of the calculated fetal requirements. She has also shown that only the best diets can supply the demands of the maternal organism in the latter months of gestation so that a diet deficient in iron is more apt to be of significance in this type of anemia than in the idiopathic form. The similarity of this anemia to the idiopathic form, and the apparent transition of one to another, certainly point to their being the same disease. In one, the iron is lost through menstruation, in the other, through fetal requirements, and in both there is a deficient absorption of iron because of achlorhydria.

Iron Metabolism. It has been assumed that faulty metabolism of iron, aside from improper absorption, may be a causative factor in some cases of idiopathic hypochromic anemia. We have found no concrete evidence in the literature to support this hypothesis, and in our own studies have accumulated some evidence against it. Comparing the retention of iron in cases of idiopathic hypochromic anemia and of chronic hemorrhagic anemia receiving the same amount of iron and ammonium citrates, it was found that there was no essential difference; in fact, the idiopathic cases retained a slightly higher percentage of the administered iron than did the others.¹¹ As was pointed out, however, the highest retention in the cases with hemorrhage was so close to that of the lowest retention in the idiopathic cases that the difference in the averages of the two groups is probably of no consequence. There was no significant disparity in the rapidity of hemoglobin formation nor in the percentage of the iron used in hemoglobin formation. In Table 2 are shown the percentage of iron retained, the percentage utilized in hemoglobin formation, and the daily hemoglobin increase in each of 3 cases of idiopathic and of chronic hemorrhagic anemia. These results were obtained in cases which were studied¹¹ over a sufficiently long time for the hemoglobin regeneration to be of significance. Since there was no difference in the iron retention nor in the utilization of this iron in the formation of hemoglobin, there can be no significant alteration in the metabolic processes related to iron utilization.

Treatment. The treatment of idiopathic hypochromic anemia consists in the administration of adequate amounts of iron in a

suitable form.²¹ It does not differ from the treatment of chronic hemorrhagic anemia, nor the hypochromic anemia of pregnancy except for the fact that a less rapid hemoglobin response may occur in cases with achlorhydria. Strauss²¹ has given the following dosages for the commonly used iron preparations: Reduced iron 3 gm., ferrous carbonate 4 gm., iron and ammonium citrates 6 gm., and ferrous sulphate 1 gm. Iron and ammonium citrates have also been recommended in dosages as high as 9 gm. per day. Minot and Heath¹⁸ have presented a standard for the expected reticulocyte response with iron administration, and Heath¹⁴ has emphasized the factors which must be controlled in any accurate clinical investigation of the results of iron therapy. He regards a rise of 0.16 gm.

TABLE 2.—IRON RETENTION AND UTILIZATION. IRON INTAKE, 500 MG. DAILY
Chronic Hemorrhagic Anemia.

Case.	Original Hb.	Fe retained, %.	Average daily Hb. increase.	Fe utilized, %.
1	4.34	27.8	0.113	3.2
2	1.55	36.4	0.041	1.2
3	7.68	43.6	0.117	3.4
Average		35.9	0.090	2.6

Idiopathic Hypochromic Anemia.

1	6.01	51.4	0.056	1.62
2	6.17	71.3	0.037	1.09
3	4.62	50.5	0.117	3.42
Average		57.7	0.070	2.06

of hemoglobin per day as the lower limit of a satisfactory response when the initial hemoglobin is below 7.8 gm. per 100 cc. of blood.¹⁴ There was considerable variation in the amount of iron required to produce this response, and the amount was greater in cases of idiopathic hypochromic anemia than in cases due to chronic hemorrhage.

In experiments on the retention of iron, which are of necessity confined to a relatively small group of cases, we have used iron and ammonium citrates exclusively. When this is administered in a dosage of 3 gm. per day, yielding approximately 500 mg. of metallic iron, the hemoglobin response fell short of the optimum response of Heath. In occasional periods and in certain subjects the response reached this minimum figure, but the average daily increase for the entire period of observation was below this amount. In Table 3 are given the original hemoglobin concentrations, the daily hemoglobin response, and the daily iron retention. It will be noted that there was no definite correlation between the amount of iron retained and the hemoglobin increase. The gastric acidity did not influence the results in this series of cases, and a satisfactory reticulocyte response was obtained in each instance.

Similar studies were carried out in another group of patients to whom only 1 gm. of iron and ammonium citrates was given each day.

Only 3 of these patients were under observation long enough for their hemoglobin response to be of significance, but in these a fairly rapid increase was obtained in spite of the small amount of iron being administered (Table 4).

When these results are viewed in the light of Heath's work, it would appear that the amount of iron being administered was less than the optimal amount. A rapid increase in hemoglobin is advis-

TABLE 3.—IRON RETENTION. IRON INTAKE, 500 MG. PER DIEM.

Case.	Gastric acidity.	Average daily iron retention, mg.	Per cent of iron retained.	Average daily hemoglobin increase, gm.	Reticulo-cytes, highest reading.	Original hemoglobin, gm. per 100 cc.
1 . . .	0	368 9	71 3	0 037	3 4	6.17
2 . . .	0	188 9	36 4	0 042	10 5	1 55
3 . . .	Normal	123 4	51 4	0 056	1.4	6 01
4 . . .	Low	151 0	31 6	0 092	2 0	5 68
5 . . .	Low	72 5	14 0	0 095	2 0	5 56
6 . . .	Low	140 8	27 8	0 113	5 4	4 37
7 . . .	0	225 2	43 6	0 117	1 6	7 68
8 . . .	0	261 2	50 5	0 117	8 9	4 62

able in the early stage of therapy and undoubtedly the larger amounts of iron should be employed. However, it is seen from these tables that relatively large amounts of iron were being retained and a fairly rapid hemoglobin rise occurred from these smaller doses of iron. This was especially true when 3 gm. of iron and ammonium citrates per day were being administered; but even with 1 gm. per day, sufficient iron was retained not only for hemoglobin formation

TABLE 4.—IRON RETENTION IRON INTAKE, 170 MG. PER DIEM.

Case.	Gastric acidity.	Average daily iron retention, mg.	Per cent of iron retained.	Average daily hemoglobin increase, gm.	Reticulo-cytes, highest reading, %.	Original hemoglobin, gm. per 100 cc.
1 . . .	0	44 7	27 1	0 082	1 0	7.36
2 . . .	Normal	42 6	23 2	0 100	2 8	4 15
3 . . .	Normal	82 2	45 1	0 151	5 4	7.80

but also for replenishment of the reserve supply of the body. It was shown that a large percentage of the retained iron was not used immediately in hemoglobin formation, but was stored elsewhere in the body.^{11,12} These results indicate that sufficient iron may be retained from these moderate amounts of iron and ammonium citrates to produce a relatively rapid hemoglobin response as well as to replace the depleted iron stores of the body, and these amounts would seem to be adequate in cases where continued iron administration is necessary over a long period of time after the hemoglobin level has returned to approximately normal.

Hydrochloric acid was given to patients receiving a normal iron intake as well as to those receiving 500 mg. of iron per day. The addition of this acid did not increase the iron retention nor the rapidity of hemoglobin regeneration.^{1c}

Iron retention experiments were carried out with the metal

administered in combination with copper and with a liver fraction.^{1b} It was found that copper, when given with a relatively small amount of iron (approximately 250 mg. per day), produced a marked diminution in the amount of iron retained by the body, but when given with larger amounts of iron (approximately 500 mg. per day), it had no appreciable effect on the storage of iron. In neither case was the hemoglobin response more rapid than was obtained by the use of iron alone. The addition of a liver fraction had a negligible effect on both iron retention and hemoglobin regeneration. From these results it appears that the addition of copper or a liver fraction is unnecessary in the treatment of hypochromic anemias and this is in agreement with the conclusions reached by Bethell.² It is possible that copper is essential in hemoglobin formation;⁸ but if so, sufficient amounts are obtained from the food, and as a contaminant of iron salts, so that additional amounts are unnecessary. Keefer¹⁶ has shown that certain cases of hypochromic anemia respond better when iron is administered in combination with a liver fraction, but we did not encounter such a case.

The administration of iron is frequently recommended by medical texts to all types of chronic diseases complicated by a "secondary" or hypochromic type of anemia. It has been shown by Heath,¹⁴ Wintrobe,²⁵ and others that the hemoglobin response to iron is negligible in many of these cases. We have followed the reticulocyte and hemoglobin response in cases of chronic nephritis, carcinoma uncomplicated by hemorrhage, lymphoma, leukemic and aleukemic myelosis, subacute bacterial endocarditis, rheumatic heart disease, and hyperparathyroidism during the administration of iron, and found no response. We believe that there is no justification for its administration in such cases.

The parenteral administration of iron has been recommended in certain instances. Heath¹⁵ has reported that the amount of iron given parenterally corresponds closely to the amount of iron gained in the circulating hemoglobin, and in his cases found an average utilization of 96%. He found that 32 mg. of metallic iron given parenterally was equivalent to 1000 mg. given by mouth. We have determined iron balances on 4 patients to whom the iron was administered intramuscularly.^{11b} It was found that although the patients retained the iron when given in a dosage of 12.3 mg. per day in the form of iron and ammonium citrates, none of the 4 showed a significant increase in hemoglobin. Two of the patients were subsequently given 500 mg. of iron per day by mouth, and a satisfactory hemoglobin response ensued. Another patient with ulcerative colitis and an inability to tolerate orally administered iron, received iron intramuscularly with no hemoglobin or reticulocyte response. From our experience, we do not feel that this amount of intramuscular iron is of benefit. We have tried larger amounts, 32 mg. per day, but generalized reactions were so severe that its administration was discontinued. Our conclusions agree with those of Broek⁴

who states that "there is never any indication for injections of iron in the treatment of anemia."

Comment. We have considered the various theories which have been proposed to explain the occurrence of idiopathic hypochromic anemia, and briefly discussed these in the light of experimental evidence obtained during the course of iron retention experiments. From the data presented, we believe that idiopathic hypochromic anemia is essentially due to chronic blood loss, either through normal or excessive menstruation, more frequently the latter, occurring in a patient in whom there is a deficient absorption of iron due to achlorhydria. This leads to a depletion of the normal iron stores in the body, and consequently to a diminished production of hemoglobin, and so to anemia. The hypochromic anemia of pregnancy is essentially the same disease and is produced by the fetal requirements for iron depleting the maternal supplies. This type of anemia not infrequently merges into a typical picture of the so-called idiopathic form. Evidence is presented to show that no derangement of iron metabolism exists in these individuals with idiopathic hypochromic anemia.

With this information, the term "idiopathic" is no longer applicable to this disease, but its use has become so firmly entrenched that it will be difficult to change. Many other terms which have been applied to the condition have obvious disadvantages. The term "simple achlorhydric anemia"²³ is the most satisfactory and should include not only those cases now termed as "idiopathic" but also those cases of menorrhagia and other chronic forms of hemorrhage in which a deficiency in the gastric secretion is present.

Our experiments have demonstrated that a large amount of iron is retained when iron and ammonium citrates are administered in a dosage of 3 gm. per day and agree with the results of Brock and Hunter.⁵ The hemoglobin response to this amount of iron is not as rapid as is obtained with larger amounts of iron. With even smaller amounts of the drug, 1 gm. per day, the iron retention is quite large and a fairly rapid increase in hemoglobin ensues. These dosages must be considered as suboptimal when compared to the results of Heath, and larger amounts of iron are undoubtedly advisable early in the course of therapy, especially in the more severe grades of anemia.

It has been repeatedly emphasized that the most satisfactory results in the treatment of this type of anemia are obtained with the use of massive doses of iron, and our results are in no way contradictory to this belief. They do show, however, that a hemoglobin response ensues when smaller amounts of iron are used, so that the massive doses need not be continued indefinitely in order to maintain a satisfactory level. The reasons for the more rapid hemoglobin response which is obtained with excessive amounts of iron has not been adequately explained. We have shown that the amount of iron retained from the smaller doses would be adequate for a satisfactory

response if it were efficiently utilized in the production of hemoglobin. Our results and those of Brock⁵ show an excessive retention of iron when larger amounts of iron are administered. Brock⁴ has discussed the efficacy of excess iron in more detail and presents evidence that "excess" iron is more effective than "enough" iron, but concludes that "there is at present no rational explanation of the necessity for such large doses."

The addition of copper or of a liver fraction did not increase the rapidity of hemoglobin regeneration in these cases nor did the administration of hydrochloric acid prove to be of benefit. The use of parenterally administered iron in a tolerated dose did not lead to hemoglobin regeneration.

Summary. 1. Idiopathic hypochromic anemia, in most cases, is a chronic hemorrhagic anemia due to menstrual blood loss and an improper absorption of iron due to deficient gastric secretion. There is no evidence of faulty iron metabolism.

2. "Simple achlohydric anemia" is therefore a preferable term.

3. Massive doses of iron produce a more rapid hemoglobin response in hypochromic anemia than do smaller amounts, although 1 gm. and 3 gm. of iron and ammonium citrates per day produce a fairly satisfactory increase in some cases even though achlorhydria is present. These amounts lead to a storage of iron in addition to that used in hemoglobin formation.

4. Neither copper nor a liver fraction, when given in addition to the iron, increased the rapidity of hemoglobin production.

5. Iron, administered intramuscularly in a tolerated dose, did not produce a hemoglobin response.

REFERENCES.

- (1.) Barer, A. P., and Fowler, W. M.: (a) *Am. J. Obst. and Gynec.*, 31, 979, 1936; (b) *Arch. Int. Med.*, 60, 474, 1937; (c) *Ibid.*, 59, 785, 1937. (2.) Bethell, F. H., Goldhammer, S. M., Isaacs, R., and Sturgis, C. C.: *J. Am. Med. Assn.*, 103, 797, 1934. (3.) Bloomfield, A. L.: *Arch. Int. Med.*, 50, 328, 1932. (4.) Brock, J. F.: *Brit. Med. J.*, 1, 314, 1937. (5.) Brock, J. F., and Hunter, D.: *Quart. J. Med.*, 6, 5, 1937. (6.) Coons, C. M.: *J. Biol. Chem.*, 97, 215, 1932. (7.) Editorial, *J. Am. Med. Assn.*, 105, 1917, 1935. (8.) Elvehjem, C. A.: *Physiol. Rev.*, 15, 471, 1935. (9.) Faber, K., and Grim, H. C.: *Arch. Int. Med.*, 34, 658, 1924. (10.) Farrar, G. E., and Goldhammer, S. M.: *J. Nutr.*, 10, 241, 1935. (11.) Fowler, W. M., and Barer, A. P.: (a) *Arch. Int. Med.*, 59, 561, 1937; (b) *The Retention and Utilization of Iron Administered Intramuscularly* (in press). (12.) Fowler, W. M., Barer, A. P., and Spielhagen, G. F.: *Arch. Int. Med.*, 59, 1024, 1937. (13.) Gordon-Taylor, G., Hudson, R. V., Doods, E. C., Warner, J. L., and Whitby, L. E. H.: *Brit. J. Surg.*, 16, 641, 1928-29. (14.) Heath, C. W.: *Arch. Int. Med.*, 51, 459, 1933. (15.) Heath, C. W., Strauss, M. B., and Castle, W. B.: *J. Clin. Invest.*, 11, 1293, 1932. (16.) Keefer, C. S., and Yang, C.: *Arch. Int. Med.*, 48, 537, 1931. (17.) Meulengracht, E.: *Acta med. Scandinav.*, 78, 387, 1932. (18.) Minot, G. R., and Heath, C. W.: *AM. J. MED. SCI.*, 183, 110, 1932. (19.) Ohlson, M. A., and Daum, K.: *J. Nutr.*, 9, 75, 1935. (20.) Strauss, M. B.: *AM. J. MED. SCI.*, 180, 818, 1930. (21.) Strauss, M. B.: *J. Am. Med. Assn.*, 107, 1633, 1936. (22.) Strauss, M. B., and Castle, W. B.: *AM. J. MED. SCI.*, 185, 539, 1933. (23.) Van der Hoof, D., and Davis, D.: *Ibid.*, 184, 29, 1932. (24.) Waugh, T. R.: *Arch. Int. Med.*, 47, 71, 1931. (25.) Wintrobe, M. M.: *Ibid.*, 54, 256, 1934. (26.) Wintrobe, M. M., and Beebe, R. T.: *Medicine*, 12, 187, 1933. (27.) Witts, L. J.: *Guy's Hosp. Rep.*, 80, 253, 1930.

STUDIES ON THE ANEMIA OF CHRONIC GLOMERULO- NEPHRITIS AND ITS RELATIONSHIP TO GASTRIC ACIDITY.*

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CECONI⁹ in 1905 was one of the first to suggest that the anemia of nephritis was probably due to a deficiency of the hematopoietic system caused by retained toxins. Since then many investigators have reiterated this theory. Brown and Roth⁵ pointed out the lack of correlation between the anemia and blood loss or excessive hemolysis. Parsons²⁷ and recently Klemperer and Otani,¹⁷ Misske and Otto²³ and others have demonstrated that the anemia develops particularly in the active stages of chronic glomerulonephritis and becomes accentuated as the renal insufficiency and retention of nitrogenous products become more marked. The most popular theory of the production of the anemia seems to be that it is due to depressed hematopoietic activity dependent on the toxic injury, occurring with the renal breakdown.

In the last decade, the study of gastric acidity has become an essential part of the study of any anemia, but most workers have neglected this important phase in their investigations on the anemia of nephritis. The few isolated studies on gastric secretion in nephritis have failed not merely to include uniform methods of determining the gastric acidity but also to present uniform conclusions. Biernacki,⁴ von Noorden,²⁶ Leist and Welkmann¹⁹ and others^{10,12,13,15,18,20,21} have found variable degrees of gastric acidity in cases of nephritis. Collectively, their studies revealed that 60% of their cases showed a diminution of the free acid present. No attempt has been made by anyone, as far as we can discover, to show any correlation between gastric acidity and the anemia.

Practically all previous investigations on the anemia of nephritis have been made with consideration only of the red cell counts, hemoglobin levels, calculated uncorrected color indices and blood nitrogen figures. Berg,³ Aubertin and Yacoel² have drawn attention to certain cases with high color indices and ascribed them to an existing hyperchromic anemia. Most authors have classified the anemia

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as belonging to the "secondary group," a term which seems unsatisfactory because those formerly so classified differ widely in their findings and in response to various types of therapy. In recent years, studies on the various anemias have been made by Osgood and Haskins,^{28,29} Murphy,²⁵ Wintrobe^{30a,b} and others using a uniform hematologic technique which now allows investigators to distinguish four types of anemia; 1, macrocytic, characterized by an increase of the mean volume and hemoglobin content of the red cells; 2, normocytic, where the size and hemoglobin of the red cells are within normal limits; 3, simple microcytic, distinguished by a moderate reduction in the size and slight reduction in the hemoglobin content; and, 4, hypochromic microcytic, where the red cell count is reduced slightly but the size of the cell is small and the hemoglobin much diminished. The following table lists the values for these types of anemia:

TABLE 1.—VALUES IN FOUR TYPES OF ANEMIA (WINTROBE).

Type of anemia.	MCV* (cu. micra).	MCH* (micro- micrograms).	MCHC* (%).
Macrocytic	95-160	30-52	31-38
Normocytic	80- 94	27-32	33-38
Microcytic	72- 79	22-26	31-38
Hypochromic	50- 72	14-21	21-29

* MCV = Mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration.

Such studies have been of value in diagnosis and often in indicating the type of treatment which might be expected to produce results. Since previous studies on this phase of nephritis have failed to utilize these more accurate methods, we felt that the application of this hematologic technique to our patients would enable us to classify their anemias more definitely, might give some clue toward recognition of the fundamental defect present in the anemia of nephritis and possibly might suggest a more efficacious treatment. Besides we felt that an assessment of the gastric acidity, along with these studies might prove illuminating. Possibly they might disclose some correlation between the developing anemia, nitrogen retention, and diminishing gastric acidity. The refractory nature of the anemia to iron therapy has always been a puzzling one and suggests that such medication may fail because of a disturbed gastric secretion.

In planning this study on the anemia of nephritis, it was apparent therefore that several questions had to be answered, namely, the nature of the anemia, the type of the red blood cell, the relationship of the anemia to nitrogen retention and renal insufficiency, the state of the gastric secretion, the reason for the lack of response to iron and what evidence there is for the theory of depressed hematopoietic activity. Consequently our plan of investigation included: 1, red cell counts; 2, hemoglobin determinations; 3, cell volumes; 4, calculations of the mean corpuscular volume, mean corpuscular hemo-

globin, and mean corpuscular hemoglobin concentration; 5, blood nitrogen determinations; and, 6, gastric analysis.

Methods. Blood was withdrawn, without stasis, from the median basilic vein with a dry syringe and needle. The blood was placed in a small test tube containing powdered heparin and gently mixed by inversion, care being taken to avoid small clots.

Red cell counts were made, using standardized red blood cell counting pipettes, counting chambers and cover slips. Three independent dilutions were made, and when necessary more, counts only being used where the variations were not greater than 100,000.

Hemoglobin determinations were made using the Evelyn photoelectric colorimeter¹¹ and the methods he describes. These were checked occasionally by Van Slyke's oxygen capacity method.

Cell volumes were estimated from hematocrit tubes,* readings being made after centrifuging at 3000 revolutions per minute for 30 minutes, to obtain constant volumes.

From the values for red blood counts, hematocrits, and hemoglobin contents, the mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were calculated as follows:^{30c}

$$\text{Mean corpuscular volume (MCV)} = \frac{\text{Hematocrit \%} \times 10}{\text{Number of R.B.C. in mls.}}$$

$$\text{Mean corpuscular hemoglobin (MCH)} = \frac{\text{Gm. hemoglobin per 100 cc.} \times 10}{\text{Number of R.B.C. in mls.}}$$

$$\text{Mean corpuscular hemoglobin concentration (MCHC)} = \frac{\text{Gm. hemoglobin per 100 cc.} \times 100}{\text{Hematocrit \%}}$$

The non-protein nitrogen was determined on fasting bloods using the micro-Kjeldahl method.

Gastric analysis was performed using 50 cc. of 8% alcohol as a test meal and the total and free acidity determined by titration with 0.1 N. NaOH, using Töpfer's reagent and phenolphthalein as the indicators. Hydrochloric acid responses to the test meal were checked by histamine injection. Normal levels of gastric acidity were regarded as the equivalents of 20 cc. and 40 cc. of 0.1 N.HCl following alcohol and histamine respectively.

Unselected patients were taken from the wards and the Renal Vascular O.D. Clinic. Their ages represent all decades, 50% being under 35 years.

Of our 48 cases of chronic glomerulonephritis, 27 had red cell counts above 4,000,000 and 21 had counts below this level. The first group will be referred to as the non-anemic and the second as the anemic group.

The majority of the patients presented pallor of the skin and mucous membranes and it was surprising to find that only 43.5% of the cases had a red cell count below 4,000,000. As one would expect, the blood picture of those without anemia was a normocytic one. The average count was 4,850,000, hemoglobin 92% (14.5 gm.) and a

* Pyrex tube calibrated to hold 2 cc. and volumetrically graduated into ten divisions reading from the bottom of the tube 0-10. Each of these is further divided into ten equal graduations, with four similar graduations above the 10 mark to permit reading in case of overfilling. The total graduated distance was not over 11 cm. The total height did not exceed 12.5 cm. The inside bore of the tubing used is approximately 5 mm.

cell volume of 43.9%; the calculated mean corpuscular volume was 90, the mean corpuscular hemoglobin 29, and the mean corpuscular hemoglobin concentration 33 (Normal MCV 80-94, MCH 27-32, MCHC 33-38). However, the hemoglobin content in individual cases was at the extreme lower limit of normal and, in many cases, at the upper limit of figures associated with the microcytic type of red cell. While these non-anemic cases exhibited the necessary

TABLE 2.—RESULTS.

	Age.	R.B.C.	Hgb., %.	Hgb., gm.	Hematocrit, %.	MCV.*	MCH.*	MCHC.*	N.P.N., mg. %.	Free HCl.	Total acid.	PSP.	CO ₂ content, vols. %.
Non-anemic males:													
Average (16 cases)	12-46	4.94	96	15.1	44.6	90	30	33	34	22	31	51	50.1
Non-anemic females:													
Average (11 cases)	17-59	4.72	88	13.7	42.9	90	29	32	33	15	24	48	50.6
Anemic males:													
Case No.													
28 . . .	16	3.68	70	10.9	31.1	84	31	35	46	6	20	40	49.9
29 . . .	47	3.36	57	10.8	30.8	91	32	35	80	7	17	10	38.9
30 . . .	45	3.19	58	9.1	26.0	81	28	35	74	0	10	..	39.0
31 . . .	46	2.28	46	7.8	20.5	90	29	37	116	0	9	0	29.9
32 . . .	39	2.00	38	5.8	16.0	80	29	36	130	0	10	0	29.8
33 . . .	47	2.78	49	7.6	26.2	94	27	29	70	6	15	7	50.5
34 . . .	26	1.93	37	5.7	17.4	90	29	33	130	0	15	0	10.1
35 . . .	15	2.89	49	7.6	22.4	84	26	34	39				
36 . . .	48	3.61	67	10.4	31.2	86	28	31	58	0	15		
37 . . .	17	1.81	29	4.5	16.2	89	25	28	89	0	9	0	27.8
38 . . .	41	1.75	27	4.2	15.0	86	24	28	180	0	14	0	28.0
Average (11 cases)	15-48	2.66	48	7.7	22.8	87	28	33	92	2	13	7	33.7
Anemic females:													
Case No.													
39 . . .	18	3.81	73	11.3	34.0	89	29	33	41	0	10	30	48.2
40 . . .	34	3.39	66	10.3	32.3	95	30	31	86	3	19	2	33.5
41 . . .	69	2.74	54	8.5	26.7	97	31	32	75	0	17	0	24.0
42 . . .	66	2.18	44	6.9	19.6	90	30	32	82	0	9	0	19.4
43 . . .	59	3.50	59	9.2	31.2	89	26	29	46	0	12	15	44.0
44 . . .	47	3.59	59	9.2	32.3	89	25	28	57	16	24	40	
45 . . .	16	3.97	67	10.4	37.3	93	26	28	36	55	
46 . . .	24	3.83	61	9.5	34.8	89	25	27	36	10	18		
47 . . .	36	3.75	60	9.4	32.0	85	24	29	47	11	21	50	
48 . . .	39	3.30	55	8.6	27.5	83	26	31	105	0	17	3	49.7
Average (10 cases)	16-69	3.41	60	9.3	30.8	90	27	30	61	4	16	22	36.5

* As in Table 1.

findings for the diagnosis of chronic glomerulonephritis, as one would expect, they did not exhibit marked diminution of renal function or any degree of nitrogen retention.

The anemic group presented the characteristics of a normocytic anemia, the cell size being within normal limits. The average red count of this group was 3,010,000, hemoglobin 54% (8.46 gm.) with a cell volume of 26.6%. It will be noted that the average mean

corpuscular volume is 88, mean corpuscular hemoglobin 28, and the mean corpuscular hemoglobin concentration 31, this average fitting a true normocytic anemia. As stated above, there were a large portion of the anemic patients who had a low hemoglobin content, although the cell size was normal. Our findings of a normocytic anemia confirms Wintrobe's observations which he made on cases of nephritis included in his studies on anemia. In this group we found no cases with a definite macrocytosis.

In contrast to the non-anemic group, these patients with chronic glomerulonephritis exhibited obvious impairment in renal function and varying degrees of nitrogen retention. It is this last point, the degree of nitrogen retention, that has interested most of the previous authors in discussing the anemia of nephritis. Assuming that the anemia was due to a toxic substance, they made an effort to determine whether one of the normal metabolic products retained in blood in excessive amounts was the cause of the toxic depression of the hematopoietic activity or whether it was an unknown toxic agent which was directly responsible. They found that the retention of nitrogen bore a close relationship to the degree of anemia when individual cases were followed and used this parallelism as an argument favoring the toxic theory. As our experience in our own clinic confirmed this observation, we were interested in determining if the same relationship held for a group of cases. In Table 3 we have tried to illustrate this parallelism.

TABLE 3.—AVERAGE CHANGES OF RED BLOOD CELLS, HEMOGLOBIN AND NON-PROTEIN NITROGEN IN 48 PATIENTS WITH CHRONIC GLOMERULONEPHRITIS.

Hgb. %	100+	90-99	80-89	70-79	60-69	50-59	40-49	30-39	20-29
R.B.C.	5.21	4.78	4.57	4.29	3.86	3.28	2.53	1.96	1.78
N.P.N.	29	35	39	37	55	73	77	130	135
No. cases	10	7	7	6	4	6	4	2	2

It is readily seen that the anemia does progress and becomes accentuated as the degree of nitrogen retention increases.

In individual cases, however, we noted that the degree of anemia and the degree of nitrogen retention for one individual did not hold for another. In a small number of cases there was a definite anemia of moderate grade but without any nitrogen retention whatsoever. Similarly, there was a small number of cases with nitrogen retention but without anemia. However, the average when grouped did show a parallelism between the degree of anemia and degree of nitrogen retention. There is one objection which must be admitted and that is, that we have fewer cases in the most marked degrees of anemia. In spite of this, we feel from our experience and that of others, that the above parallelism holds.

As the degree of nitrogen retention mirrors to some extent the degree of acidosis present, there is reason to suspect that gastric secretion may be disturbed, as the plasma bicarbonate would be utilized in an attempt to regulate the acid-base equilibrium. That

plasma bicarbonate is intimately associated with formation of free hydrochloric acid in the gastric secretion was shown by the work of Apperly and Crabtree¹ and confirmed by Browne and Vineberg.⁶ With this thought in mind gastric analysis was performed on 41 of our patients. The degree of the acidity of the specimens taken 1 hour after the alcohol test meal was calculated. All responses were checked with histamine, and blood CO₂ content determinations were carried out.

In the non-anemic group, 22 out of 27 patients had a normal average gastric acidity to the alcohol test meal, 5 cases had an anacidity but showed a response to histamine. This anacidity after alcohol represents an incidence of 18.5%. In these 22 patients, we found that there was a close parallelism with the red cell count but none to the plasma bicarbonate.

In the anemic group, 19 cases were studied. Their responses to the alcohol meal were all diminished and 11 patients (57.8%) showed anacidity to alcohol stimulation and a diminished response to histamine. Five of these 11 cases had absolute achlorhydria even after histamine, an incidence of 26.3% of the 19 cases studied. The carbon dioxide content (plasma bicarbonate) in the anemic group varied from 10 to 50 vols. %, but the most striking feature occurred in the 5 cases with absolute achlorhydria. In these patients the CO₂ content was below 30 vols. %. Browne and Vineberg,⁶ using dogs, found that experimentally when the CO₂ content was lowered below 30% that nervous stimulation failed to produce a secretion of free acid. In a small number of cases of chronic glomerulonephritis we have found proof that there is no secretion of hydrochloric acid when the CO₂ content falls below 30% and also that there is a disturbance in gastric secretion even above this level, although there is no relationship to the plasma bicarbonate to indicate that any disturbance in its value is responsible for the diminution of the free hydrochloric acid present.

In Table 4 we have tried to illustrate the relationship between

TABLE 4.—AVERAGE CHANGES OF RED BLOOD CELLS, HEMOGLOBIN AND FREE HYDROCHLORIC ACID IN 41 PATIENTS WITH CHRONIC GLOMERULONEPHRITIS.

Hgb. %	100+	90-99	80-89	70-79	60-69	50-59	40-49	30-39	20-29
R.B.C.	5.10	4.87	4.78	4.27	3.64	3.28	2.41	1.96	1.78
Free HCl	24	20	10	9.5	8	4	2	0	0
No. cases	10	5	4	5	4	6	3	2	2

red cells and hemoglobin to the free acid present in the stomach. It will be clearly seen, again acknowledging the paucity of numbers in the severe grades, that the anemia increases almost in direct relationship to the fall in gastric acidity. This is suggestive at least that the secretion of free HCl is distributed and may bear some relationship to the development of the anemia or at least to its continuance on the basis of improper absorption of materials necessary for blood formation.

It was thought at this point that bone-marrow studies might throw some light on the problem. At least one should be able to determine whether there was any absolute evidence of depressed hematopoietic function. Bone-marrow sections, 31 in all, were reviewed from postmortem material available. This group comprises 20 males and 11 females, of ages varying from 12 to 70 years, with a fairly uniform distribution of age groups. Blood counts done during the course of the disease, in the ordinary routine manner, varied between 1,430,000 and 4,700,000 with low hemoglobin contents. These cases were all clinically and pathologically consistent with the diagnosis of chronic glomerulonephritis, although in some of the older patients there existed secondary disorders not of a nature to interfere with the blood picture. The majority of these patients revealed postmortem rib marrow of a normal or hyperplastic type, and in a few cases where the femur marrow was examined, some increase in the erythropoietic activity. The hyperplasia was generally of the normoblastic type—a functional hyperplasia, commonly associated with chronic infections. In no case was there increased erythropoiesis of the megaloblastic type, such as seen in pernicious anemia, nor were there any abnormalities in the size of the medullary cavity and no evidence of bone absorption. One must bear in mind, however, that these sections are postmortem material and have all the disadvantages of such unit studies. We believe, however, that bone-marrow biopsy would reveal little difference in the histologic picture.

In seeking another possible explanation for the low gastric acidity we studied sections of stomach from 29 of these patients. The studies revealed no histo-pathologic explanation for a diminution of the gastric acidity, although many cases died in acidosis and uremia. The glands were well preserved. The most striking feature was edema of the submucosa and marked anatomical changes in the arterioles of the submucosa: these showed moderate to marked fibroblastic proliferation of the intimal layers producing variable diminution of the lumen. In rare cases, one found occasional vessels occluded by intimal thickening or a thrombus. In these latter cases superficial ulceration was common.

Discussion.—Since there is no evidence to date of increased hemolysis or increased blood loss to explain the anemia of chronic glomerulonephritis, we would expect that it would be due to one or two causes; 1, insufficiency of active blood-forming tissue, or, 2, insufficiency of material available for the production of red cells and hemoglobin.

If the anemia is due to toxic depression of bone marrow one would expect a hypoplastic or aplastic bone marrow. Our studies of post-mortem material clearly indicate that the bone marrow is either normal or hyperplastic in appearance, apparently capable of response and containing the cellular elements necessary for erythropoiesis.

This is not in agreement with the recent work of Isaacs,¹⁴ who thinks that the bone marrow in chronic nephritis is aplastic in character.

Our observations on the character of the red blood cell in the anemia of chronic glomerulonephritis permit us to classify the anemia as one of the normocytic variety; but in some of the individual cases, the hemoglobin content is slightly lower than that commonly associated with this type of anemia. A deficient supply of erythrocytic-building material might be considered the possible explanation for this type of picture. It is common knowledge that the anemia of chronic glomerulonephritis does not respond to iron and the slightly lower hemoglobin found in the individual red cell is probably of significance and compatible with our feeling that the anemia is due to a deficiency of blood-cell forming material. Our studies on the gastric acidity have tended to support this view.

Apperly and Crabtree¹ in 1931 suspected that the chemical condition of the blood had some relationship to gastric function and proceeded to show that the amount of HCl present during gastric stimulation was determined or at least bore a close relationship to the bicarbonate content of the blood plasma and could be made to vary by producing changes in the latter. This work was confirmed by Browne and Vineberg⁶ in conclusive experiments on dogs. They showed that the secretion following vagal stimulation was inhibited when the CO₂ content of arterial plasma fell below 30 vols. %. They further demonstrated that total amount of acid secreted, as well as the concentration, could be increased or decreased by artificially raising or lowering the plasma CO₂ content. Their work strongly suggests that the plasma bicarbonate is involved in some manner in the production of HCl.

In nephritis, we have a pathologic condition existing in the kidneys which prevents the normal elimination of the end products of protein metabolism and the normal regulation of the acid-base equilibrium, especially in the chronic active and terminal stages with renal insufficiency. When sufficient renal impairment occurs to produce nitrogen retention, there is also an accompanying disturbance in the acid-base control of the body and a degree of acidosis is developed which clinically is not detectible and which varies with the nitrogen retention. In these stages, as we have pointed out before, the anemia becomes most marked and progressive, the blood nitrogen increases, acidosis occurs, gastric acidity becomes lower and at a point is not secreted at all. We found, however, that often there is a lower gastric acidity than can be accounted for by the blood bicarbonate; but that in the terminal stages, when the CO₂ content was below 30 vols. %, there was complete anacidity even after the use of histamine. To us one of the most important features in the anemia of chronic glomerulonephritis is the diminished or absent HCl in the gastric secretion and this diminution must play an important part in the improper digestive processes and improper absorption of food and iron.

Gastric digestion, by virtue of the presence of free hydrochloric acid and pepsin, has a definite action in: 1, hydrolysis of protein; 2, modification of the pH of the small bowel, and, 3, as a stimulation for the secretion of pancreatic enzymes and flow of bile. These are all necessary to carry on the proper digestive processes in the remainder of the gastro-intestinal tract. Many in the past have believed that this function has not been entirely necessary for the continuous well being of patients. Surgery has taken advantage of this assumption and has performed gastric resections of varying degrees up to total gastrectomy. In the last few years, however, we have learned that many of these patients develop an anemia of various types.

Experimentally, too, in recent years gastric digestion has been shown to be of the greatest importance in relation to anemia. Castle^{7,8} and others have called attention to the absence of hydrochloric acid in the stomach in the anemias of other types and have concluded that various disturbances of the gastro-intestinal tract may interfere with digestion and absorption necessary for proper metabolism of food substances required for hematopoietic activity, even in the presence of a normal diet.

Mettier and Minot²² then indicated that soluble iron compounds are more readily absorbed in the presence of acid meals. This corresponded closely with the work of Mitchell and Miller,²⁴ who were more concerned in the most suitable pH for iron utilization. Kellogg and others¹⁶ have recently succeeded in showing that when the iron reserves of the body were depleted, a condition of hypochromic anemia results and persists in the absence of normal gastric secretion, even when an iron rich diet is ingested.

From a therapeutic standpoint, predigested acid meals, or even hydrochloric acid itself, might prove of value, except there are obvious reasons to believe that such measures would only serve to increase the acidosis present.

In conclusion, our investigations, along with the experimental work of others, seem to indicate that there is a correlation between the decreased renal function, the development of a normocytic anemia and the development of a low to absent secretion of free hydrochloric acid. The low gastric acidity, by interfering with the proper metabolism of ingested food and the absorption of iron, indirectly produces a deficiency of "building material" for sufficient red blood cell formation and the production of hemoglobin. While we have not demonstrated the etiologic factor in the production of the anemia of chronic glomerulonephritis, we have indicated reasons for the continuance of the condition and possibly one of the factors responsible for the refractory response to therapy.

Summary. 1. The anemia of chronic glomerulonephritis is normocytic in type.

2. The anemia becomes manifest as renal insufficiency occurs and increases with the degree of nitrogen retention.

3. With increasing anemia, there is a decrease in the gastric acidity.

4. Absolute achlorhydria is present when the CO_2 content of whole blood (plasma bicarbonate) falls below 30 vols. %.

5. There is no apparent lack of active blood forming tissue.

6. A discussion of the relationship between renal insufficiency, gastric acidity and the anemia has been given.

7. Reasons have been offered for the persistence of the anemia and its refractoriness to therapy.

The authors wish to acknowledge a debt of gratitude to Dr. J. P. O'Hare for his advice and helpful criticism, and to Dr. M. Pijoan for the CO_2 studies.

REFERENCES.

- (1.) Apperly, F. L., and Crabtree, M. G.: *J. Physiol.*, 73, 331, 1931. (2.) Aubertin, C., and Yacoel, J.: *Bull. et mém. Soc. méd. d. Paris*, 48, 870, 1924. (3.) Berg, B.: *Med. Rec.*, 100, 914, 1921. (4.) Biernacki, E.: *Berl. klin. Wehnschr.*, 28, 252, 1891. (5.) Brown, G. E., and Roth, G. M.: *Arch. Int. Med.*, 30, 817, 1922. (6.) Browne, J. S. L., and Vineberg, A. M.: *J. Physiol.*, 75, 345, 1932. (7.) Castle, W. B.: *Am. J. Med. Sci.*, 178, 748, 764, 1929. (8.) Castle, W. B., *et al.*: *J. Am. Med. Assn.*, 97, 904, 1931. (9.) Ceconi, A.: *Clin. med. ital.*, Milano, 44, 15, 1905. (10.) Drapper, M.: Cited by Von Noorden.²⁶ (11.) Evelyn, K. A.: *J. Biol. Chem.*, 115, 63, 1936. (12.) Fliederbaum, J., and Pianko, N.: *Klin. Wehnschr.*, 8, 1076, 1929. (13.) Fouts, P. J., Helmer, O. M., and Zerfas, L. G.: *Am. J. Digest. Dis.*, 1, 667, 1934. (14.) Isaacs, R.: *Am. J. Med. Sci.*, 193, 181, 1937. (15.) von Jassah: Cited by Von Noorden.²⁶ (16.) Kellogg, F., and Mettler, S. R.: *Arch. Int. Med.*, 58, 278, 1936. (17.) Klemperer, P., and Otani, S.: *Arch. Path.*, 11, 60, 1930. (18.) Krawkow: Cited by Von Noorden.²⁶ (19.) Leist, M., and Weltmann, O.: *Wien. Arch. f. inn. Med.*, 2, 245, 1921. (20.) McEnery, E. T., Meyer, J., and Evy, A. C.: *J. Lab. and Clin. Med.*, 12, 362, 1927. (21.) Martin, L.: *Bull. Johns Hopkins Hosp.*, 55, 57, 1934. (22.) Mettler, S. R., and Minot, G. R.: *Am. J. Med. Sci.*, 181, 25, 1931. (23.) Misske, R., and Otto, W.: *Folia Hæmatol.*, 55, 161, 1936. (24.) Mitchell, H. S., and Miller, L.: *J. Biol. Chem.*, 85, 355, 1929. (25.) Murphy, W. P., and Fitzhugh, G.: *Arch. Int. Med.*, 46, 440, 1932. (26.) von Noorden, C.: *Metabolism and Practical Medicine*, Chicago, W. T. Keener & Co., 2, 437, 1907. (27.) Parsons, L., and Ekola-Strolberg, M.: *Am. J. Med. Sci.*, 185, 181, 1933. (28.) Osgood, E. E., and Haskins, H. D.: *Ann. Int. Med.*, 5, 1367, 1932. (29.) Osgood, E. E., Haskins, H. D., and Trotman, F. E.: *J. Lab. and Clin. Med.*, 17, 859, 1932. (30.) Wintrobe, M. M.: (a) *Am. J. Med. Sci.*, 177, 513, 1929; (b) *Arch. Int. Med.*, 54, 256, 1934; (c) *J. Lab. and Clin. Med.*, 17, 899, 1932.

DEFICIENCY SYNDROMES ASSOCIATED WITH CHRONIC ALCOHOLISM.

A CLINICAL STUDY.

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LETTSOM⁸ (1787) first described alcoholic polyneuritis and attributed it to the neurotoxic effect of the alcohol. This belief remained unchallenged until Shattuck,¹² in 1928, suggested vitamin deficiency as a probable cause of the neuritis. Since then Minot,¹⁰ Wechsler,¹⁵ and Meyer⁹ have discussed the relationship of avitaminosis to this disorder. From observations of 57 cases and a study of the record

of 73 additional cases Minot, Strauss, and Cobb¹¹ concluded that dietary deficiency (B₁) played an important rôle in the production of "alcoholic" polyneuritis. In addition to inadequate intake they believed that other factors such as the states of the gastro-intestinal tract were operative in the production of the neuritis. In an excellent review, Cobb and Coggeshall¹² drew attention to the diversity of lesions in the central and peripheral nervous system of chronic alcoholics, and speculated that "the imbibing of alcohol may, by its effect on the digestive tract and the diet, precipitate neuronal degeneration (and perhaps vascular lesions) in the brain, cord or peripheral nerves. If the process is largely in the brain and peripheral nerves, Korsakoff's syndrome results. If the brain is affected severely, with less degeneration of the cord and least in the peripheral nerves, the syndrome is that of pellagra. The converse of this picture is 'alcoholic' polyneuritis, while Nonne's 'myelitis intrafunicularis' is intermediate between these two."

In this connection Spies¹³ and his coworkers have contributed significant data in respect to the similarity between endemic pellagra and "alcoholic" pellagra and the dramatic response of the latter group to vitamin B₂ therapy.

To each of 10 alcoholic addicts with polyneuritis, Strauss¹⁴ gave a pint to a quart of blended whisky daily. He supplemented a vitamin-rich diet with oral administration of yeast, and parenteral introduction of vitamin B₁ and liver. He observed that the neuritis improved as rapidly with alcohol as without it and concluded that the "alcoholic" polyneuritis did not result primarily from a direct neurotoxic effect of alcohol but was probably dependent upon dietary deficiency. Jolliffe, Colbert, and Joffe⁷ estimated the vitamin/calory ratio (Cowgill's⁴ formula) of 42 alcohol addicts, 26 of whom had polyneuritis. They demonstrated that alcohol addicts with polyneuritis failed to obtain adequate amounts of vitamin B while those without polyneuritis, though the addiction was of long duration, did obtain adequate amounts; and that certain subjects without polyneuritis consumed enough alcohol over an adequate period of time to cause peripheral nerve involvement due to the alcohol *per se*. In a later publication,⁶ these authors noted the effects on 28 alcohol addicts who had uncomplicated polyneuritis of: 1, an inadequate or borderline vitamin B diet; 2, a diet with approximately twice the estimated vitamin B requirement; and, 3, a diet with approximately 4 times the vitamin B requirement. Those in the first 2 groups showed no improvement in the course of a month; improvement was more marked in those of the 3d group than in those of the 2d.

In addition to the qualitative and quantitative studies of vitamin B deficiency in alcohol addicts with polyneuritis, Blotner² has demonstrated the inhibitory effect of alcohol on the proteolytic activity of certain gastro-intestinal enzymes *in vitro* and *in vivo*.

Since the appreciation of the avitaminotic aspects of chronic alcoholism has many practical therapeutic considerations it appeared of value to undertake a clinical study of the incidence of polyneuritis in the alcohol addicts admitted to this hospital. Particular attention was given to the dietary history, anemia, and the clinical response to vitamin B therapy.

Clinical Study. A study was made in this Hospital from September 1, 1935 to August 31, 1936, of the total number of patients admitted in whom chronic alcohol addiction had played a major rôle in causing their admission. Of the total first admission (844) during this period, 131 patients were examined (15.5%). Together with the usual physical, neurologic and psychiatric examinations, particular attention was paid to the dietary history, presence or absence of polyneuritis, anemia and clinical response to vitamin B therapy.

It is not the purpose of this paper to discuss in detail the symptomatic rôle that alcohol addiction plays in the personality instability of the individual patient. Suffice it to say, as has been noted previously,⁵ that chronic alcoholism *per se* is not a disease, rather it is a manifestation of an underlying personality maladjustment and that remedial measures to be successful must be directed at the primary and significant causal factors. Any attempt to treat chronic alcoholism must be based on an intelligent appreciation and evaluation of the endowment, the life experiences, and the specific situations in which the individual patient finds himself. This can only be done with a detailed personality analysis in the hands of well trained physicians over a long period of time and with the patient in a controlled environment.

Every patient who was studied has been addicted to the use of alcohol for varying lengths of time preceding admission to the hospital. It was extremely difficult to come to any reliable conclusion concerning the number of years of addiction. Inquiries were made in respect to quantity, quality and frequency of the liquor consumed but the data does not warrant any reliable conclusions.

Age Incidence. It is interesting to note that the age period between 30 and 50 contained over 64% of the total number (Table 1).

TABLE 1.—AGE INCIDENCE OF TOTAL NUMBER OF PATIENTS.

21 to 30	16
31 to 40	44
41 to 50	41
51 to 60	20
61 to 70	8
71 to 80	2

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Sex Incidence. Of the 131 cases, 16 (12.2%) were female. Although this small number does not warrant any valid statistical conclusions, the age incidence when divided as to sex reveals a

relative increase in the number of females of a later age period (41 to 50) as compared with the males and with the total number.

TABLE 2.—SEX INCIDENCE.

	Female.	Male.
21 to 30	3	13
31 to 40	4	40
41 to 50	8	33
51 to 60	1	19
61 to 70	8
71 to 80	2
	<hr/> 16	<hr/> 115

Mental Status. Ebaugh and Romano⁵ have discussed the inadequacies of the present classification of the alcoholic psychoses. The various dramatic incidents that are experienced by chronic alcoholics such as pathologic intoxication, delirium tremens, acute and chronic alcoholic hallucinosis and Korsakoff's psychosis have addiction to alcohol as a common denominator although the presence or absence of personality predisposition, more profound mental instability and somatic factors (avitaminosis) may have a more important causal relationship. This classificatory inadequacy is most evident in a consideration of chronic alcoholism, uncomplicated by the previously noted psychotic incidents. Previous concepts of "chronic deterioration," "alcoholic paranoia" and others have only provoked further confusion. An attempt⁵ has been made to divide this group into etiologic divisions, although this is far from being satisfactory.

TABLE 3.—INCIDENCE OF PSYCHOSES.

	Male.	Female.
Pathological intoxication	1	0
Chronic alcoholism with mental deficiency (moron) . . .	0	1
Chronic alcoholism with senile dementia	2	0
Chronic alcoholism with Korsakoff's psychosis	2	5
Chronic alcoholism with manic-depressive depression . .	3	1
Chronic alcoholism with schizophrenia	8	0
Chronic alcoholism with cerebral arteriosclerosis . . .	11	0
Chronic alcoholism with psychosis	14	0
Chronic alcoholism with delirium tremens	18	3
Chronic alcoholism without psychosis	56	6
	<hr/> 115	<hr/> 16

Dietary History. Attention was paid to the quantity and quality of the patient's diet. While it was almost impossible to secure reliable data in respect to the dietary history during the total period of addiction an attempt was made to investigate the peculiarities of the food intake for the period preceding admission. Informants as well as the patient were contacted for these data. By the arbitrary divisions of mild, moderate, and severe are understood qualitative dietary inadequacies for periods varying between 2 weeks and 6 months preceding hospital admission. The accompanying tables show that 11 (68.7%) of the females and 64 (55.6%) of the males had some qualitative inadequacy in their diets for varying

periods previous to admission. It is more pertinent to remark that of the 77 patients (58% of total number) who showed evidence of some form of neuritis 61 (79%) gave a history of inadequate diets.

TABLE 4.—INCIDENCE OF DIETARY INADEQUACY.

	Male.	Female.
No data	33	2
Normal	18	3
Mild	39	2
Moderate	22	3
Severe	3	6
	<hr/> 115	<hr/> 16

Incidence of Polyneuritis. Although it is difficult to divide or classify the severity of the neuritides observed, it was thought expedient to introduce arbitrary divisions of mild, moderate and severe. Obviously, what was interpreted as mild on one examination may have been designated moderate or severe in following examinations. However, the neurologic status on admission as interpreted by one examiner was considered the basis for the classification. By mild is understood the presence of pain, deep muscle tenderness and weakness, superficial hyperesthesia and exaggerated deep reflexes. With increased weakness, persistent deep muscle pain, beginning muscle atrophy, paresthesia, disturbance of position and vibration senses and loss of deep reflexes, a moderate degree of involvement is present. Muscle atrophy or paralysis, with or without contractures, "glove and stocking" anesthetic areas, vibration and position sense disturbances and absence of deep reflexes constituted the more advanced or severe degree of nerve involvement. In the severely involved of the female group, 5 of the 6 experienced a Korsakoff's psychosis. Dermatitis with pigmentation, glossitis, and stomatitis together with intractable diarrhea were observed in 4 of these 5 and suggested deficiency of vitamin B₂. While spongy gums were observed frequently in both male and

TABLE 5.—INCIDENCE OF POLYNEURITIS.

	Male.	Female.
Normal	48	6
Mild	31	2
Moderate	22	2
Severe	14	6
	<hr/> 115	<hr/> 16

female patients no definite clinical evidences of scurvy were noted. Unfortunately, gastric analyses were not done of the majority of the patients studied and the conclusions do not warrant mention. Ten (62.5%) of the female patients, 67 (58.2%) of the male patients suffered from some degree of peripheral nerve involvement. Of the total number of patients studied (131), 77 (58%) presented evidences of neuritic involvement.

Anemia. Accepting the standards as determined by Andresen and Mugrage¹ for red blood cell values for normal men and women in this region, the initial red blood cell count and hemoglobin determination (Sahli) taken on admission were collected in order to determine the incidence of anemia in these patients. The following are the standards that were used for comparison (Table 6.)

TABLE 6.—ANEMIC STANDARDS.

	Men				Women			
	Normal.	Mild.	Moderate.	Severe.	Normal.	Mild.	Moderate.	Severe.
Hemoglobin (grams) Sahli	14.0-19.0 mean 16.5	12 0-14 0	10.0-12 0	Below 6	12 5-16.5 mean 14 5	11 5-12 5	9-11.5	Below 6
Red blood corpuscles (millions)	4 7- 6 2 mean 5.4	4 4- 4 7	3 4- 4 4	Below 2	4 2- 5 1 mean 4 6	3 8- 4 2	3 0-3 8	Below 2

Eleven (68.7%) of the female patients, and 64 (55.6%) of the male patients suffered from some degree of anemia, although 56 of the total number of patients (75) with some degree of anemia had only mild involvement. Of the 19 patients who had moderate or severe anemia, 6 (8% of the 75 patients with anemia) had macrocytosis as revealed by increased cell diameter and volume index.

Iron and ammonium citrate in large daily doses (4 to 8 gm.) together with parenteral liver were successful in treating the anemias.

TABLE 7.—INCIDENCE OF ANEMIA.

	Male.	Female.
Normal	51	5
Mild	50	6
Moderate	12	4
Severe	2	1
	<hr/> 115	<hr/> 16

Clinical Response to Vitamin B Therapy. Every patient with either mild, moderate or severe peripheral nerve involvement was placed on a high-caloric, high-vitamin diet (4000 to 5000 calories daily) increasing the quantity of lean-meat protein and decreasing carbohydrate. This diet was supplemented with dried brewer's yeast tablets (4 gm. daily), wheat-germ preparations (30 to 60 gm. daily) and either vitamin B₁ or liver* preparations given parenterally in daily doses. In addition to this, fresh orange or tomato juice together with various preparations of cod-liver oil or haliver oil were given.

In the more severe neuritides associated with Korsakoff's psychoses, forced feedings were resorted to and the parenteral liver dosage was increased (2 to 4 cc. daily).

Due to the variation in severity of the lesions, the individualiza-

* Courtesy of Eli Lilly & Co., Indianapolis.

tion of therapy and the relatively limited stay of the patients (average 24.67 days) adequate quantitative data are not available. However, a rough clinical estimate of no change, partial improvement and total improvement was tabulated. Seventy-seven patients (58% of the total number) revealed some evidence of polyneuritis; 5 (6.4%) showed no clinical response to therapy while they were under observation; 47 (61%) showed partial improvement and 25 (32.4%) showed complete improvement.

TABLE 8.—RESPONSE OF THE PATIENTS WITH MILD POLYNEURITIS TO VITAMIN B THERAPY.

	Mild P.	Moderate P.	Severe P.
No change	2	2	1
Partial improvement	14	14	19
Total improvement	17	8	0
	<hr/> 33	<hr/> 24	<hr/> 20

Summary. One hundred and thirty-one chronic alcoholics (15.5% of the total hospital admissions (844) in 1 year) were studied in respect to the incidence of polyneuritis, with particular attention to dietary history, anemia and response to vitamin B therapy.

Of these chronic alcoholics 77 (58%) presented some degree of neuritis.

A history of inadequate food intake previous to admission was obtained in 61 (79% of those showing polyneuritis).

Some degree of anemia was present in 75 (57% of the chronic alcoholics), although 56 (74.6%) had only mild involvement.

Of the 77 patients with neuritis, 5 (6.4%) failed to respond to vitamin therapy, 47 (61%) showed partial improvement, and 25 (32.4%) showed complete improvement with specific therapy during their period of hospitalization.

Conclusion. Vitamins B₁ and B₂ are of definite value in the treatment of the deficiency syndromes associated with chronic alcoholism.

REFERENCES.

- (1.) Andresen, M. L., and Mugrage, E. R.: Arch. Int. Med., 58, 136, 1936. (2.) Blotner, H.: J. Am. Med. Assn., 106, 1970, 1936. (3.) Cobb, S., and Coggeshall, H. C.: Ibid., 103, 1608, 1934. (4.) Cowgill, G. R.: The Vitamin B Requirement of Man, New Haven, Yale University Press, 1935. (5.) Ebaugh, F. G., and Romano, J.: The Alcoholic Psychoses. To be published in Piersol's Cyclopedia of Medicine, F. A. Davis Company, Philadelphia, 1937. (6.) Jolliffe, N., and Colbert, C. N.: J. Am. Med. Assn., 107, 642, 1936. (7.) Jolliffe, N., Colbert, C. N., and Joffe, P. M.: Am. J. Med. Sci., 191, 515, 1936. (8.) Lettsom, J. C.: Mem. Med. Soc., London, 1, 128, 1779-1787. (9.) Meyer, A.: Schweiz. med. Wehnschr., 62, 1243, 1932. (10.) Minot, G. R.: Ann. Int. Med., 3, 216, 1929. (11.) Minot, G. R., Strauss, M. B., and Cobb, S.: New England J. Med., 208, 1244, 1933. (12.) Shattuck, G. C.: Am. J. Trop. Med., 8, 539, 1928. (13.) Spies, T. D.: Am. J. Med. Sci., 184, 837, 1932. (14.) De Wolf, H. F.: Ibid., 186, 521, 1933; J. Am. Med. Assn., 104, 1377; 105, 1028, 1935; Blankenhorn, M. A.: Trans. Assn. Am. Phys., 50, 164, 1935; Arch. Int. Med., 56; 920, 1935; Chinn, A. B.: J. Clin. Invest., 14, 941, 1935; Blankenhorn, M. A.: J. Am. Med. Assn., 107, 641, 1936; Chinn, A. B., and McLester, J. B.: Ibid., 108, 853, 1937. (15.) Strauss, M. B.: Am. J. Med. Sci., 189, 378, 1935. (16.) Wechsler, I. S.: Med. J. and Rec., 131, 441, 1930; Arch. Neurol. and Psychiat., 29, 813, 1933.

CASE FINDING IN TUBERCULOSIS, AN ADULT PROBLEM.*

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CASE finding in tuberculosis has been the keynote of the anti-tuberculosis campaign for the past 30 years or more. Throughout this period we have placed increasing emphasis on early diagnosis, but until recently we have made little progress in this direction. The average tuberculosis program involves the examination of contacts to known cases. This is the best and most productive source of case finding thus far developed. Considerable time and emphasis has been placed on routine tuberculin testing and the Roentgen ray in grade-school populations. To date we have accumulated a vast amount of information from such studies. They have been the means of finding many new cases, but if evaluated in the light of the relative yield for the dollar invested there is much reason to question its value, especially if such a plan is the predominant effort at case finding and control in the community.

Fortunately, we are able to clearly evaluate our problem in tuberculosis. It may be done by simple statistical analysis of our cases and deaths by age groups, sex, occupation or other major divisions. The plotting of these data at once indicates a typical curve for either sex. Among females since 1900 we note in general a definite decrease for all ages and for the individual age groups. There is this difference, however, the peak of mortality has shown a tendency to shift forward, so that where it was reached at about the age of 35 in 1900 it is now reached at 25 years. Furthermore, after the sharp rise beginning at 15 years there is now a tendency to flatten out and remain more or less constant for the remaining years of the life cycle.

For males we have always noted a much higher rate than among females. In the past 30 years there has been a sharp decline for all ages as well as for the various age periods. In contradistinction to the female curve we note that the peak in mortality in 1900 was at 45 years and in 1930 it has shifted back to 60 years. Also the peak among males is much sharper and falls more abruptly afterward than that for females.

If a similar analysis is made for white and colored we at once note a sharp distinction between the two. The white is invariably lower than the colored.

On the basis of tuberculous infection throughout all age periods, we find the lowest rates at infancy and they continue to rise as the years advance. The literature and experience on this point are too voluminous and well known to demand specific reference in this discussion.

* Read before American Academy of Tuberculosis Physicians, Atlantic City, N. J., June 8, 1937.

Our knowledge of the pathogenesis of tuberculosis follows closely the same general plan. If the infant survives his third year without succumbing to tuberculosis, in all probability he will not develop a reinfection type until he has reached adolescence, after which

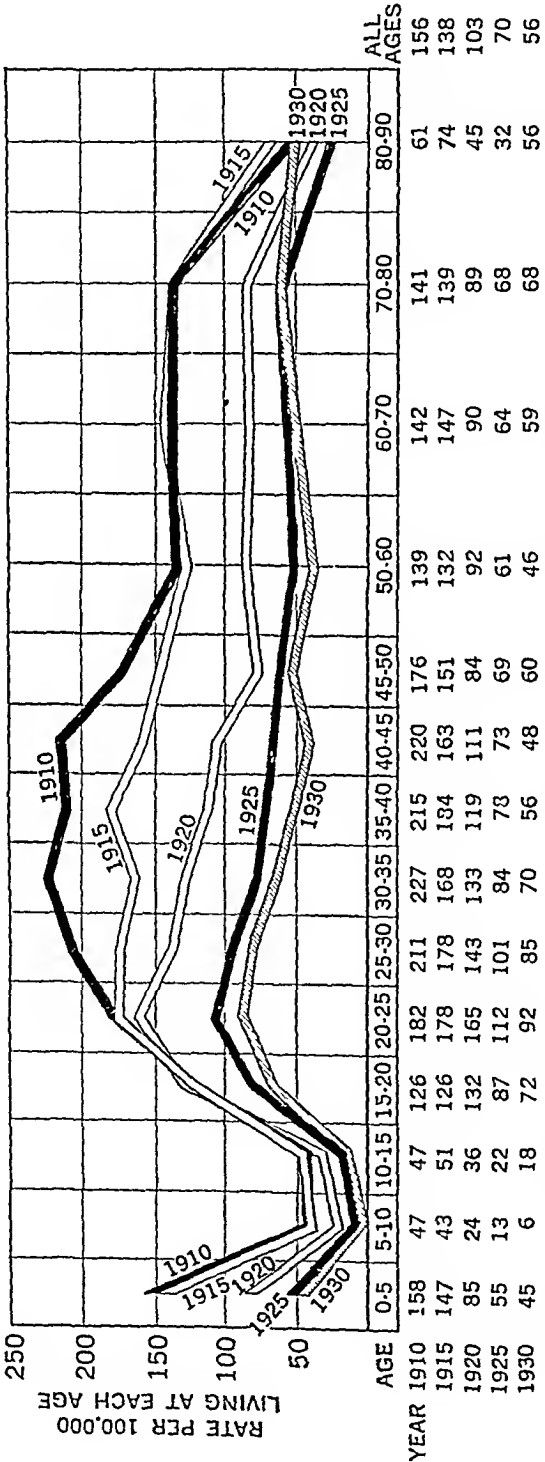


FIG. 1.—FEMALE TUBERCULOSIS (ALL FORMS) DEATH RATE by Age in New York City, 1910, 1915, 1920, 1925, 1930.

time our morbidity curves show a sharp rise which culminates in the peaks described above.

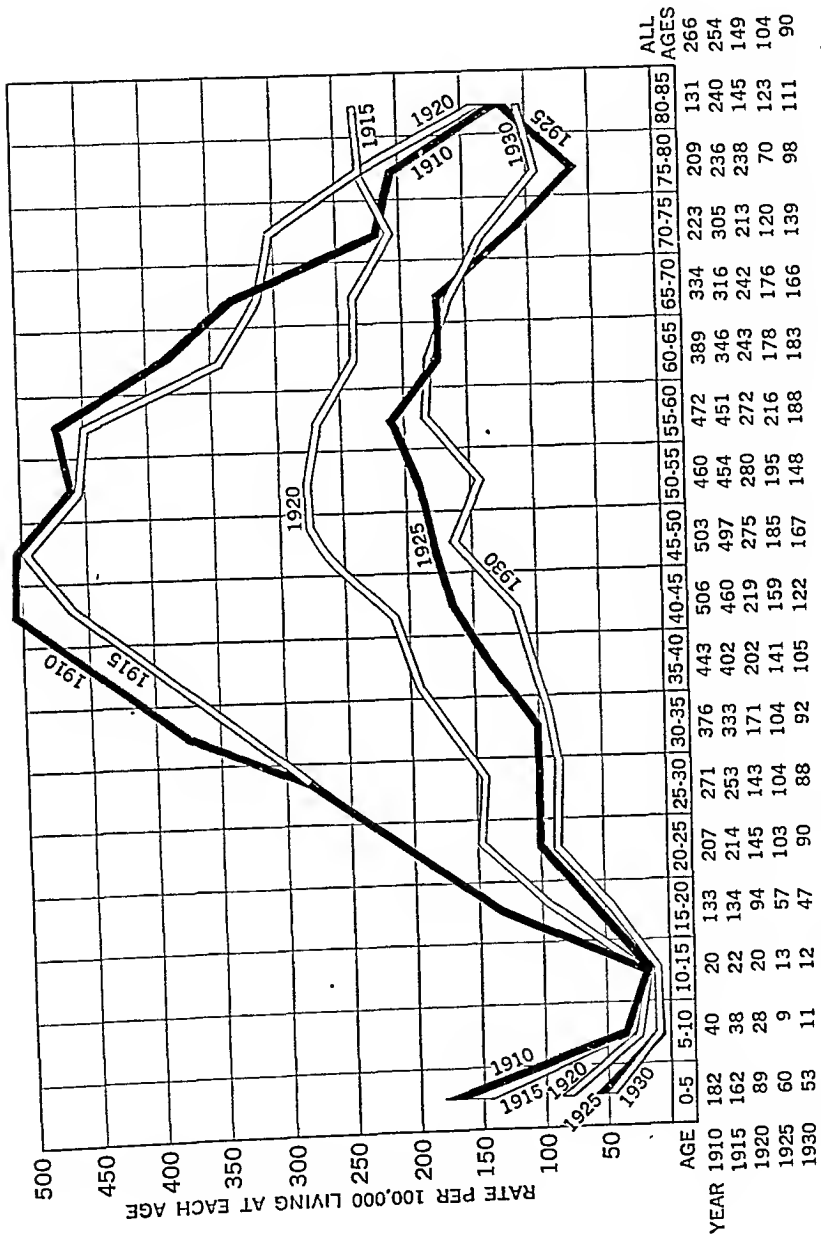


FIG. 2.—MALE TUBERCULOSIS (All Forms) Death Rate by Age in New York City, 1910, 1915, 1920, 1925, 1930.

Thus all available data on tuberculosis clearly indicates that it is a disease of adult life. It is during that period that we are confronted with problems of debility and death and the spread of

infection to infants as well as children and adults. It will naturally follow therefore that the greatest achievements in case finding and thereby tuberculosis control must be expected from the adult groups. During the passing years our increased knowledge of the prevalence of tuberculosis has been reflected very definitely in our diagnoses; we are no longer content to accept a diagnosis of chronic bronchitis or bronchial asthma in the aged, for all too frequently it has been such cases that have been responsible for the continued spread of the disease to others.

It has been fairly common practice in most communities to find that from 5 to 20 or more per cent of new cases reported are diagnosed first at or within a month or so of death. It is logical to assume that those cases have been suffering with tuberculosis from 2 to 5 or more years, during which time they have undoubtedly had an opportunity to widely disseminate their disease to others. Because the nature of their illness is unknown their menace to close contacts and associates is all the more important. It is in part from this group that we are continually reaping our annual crop of new cases. It is also the answer for the difficulty encountered in tracing the source case in many new cases diagnosed.

Another cause for our lack of success in early diagnosis is to be found in the fact that by and large we have placed emphasis chiefly on the basis of symptoms. Here again we have abundant evidence to show that in early disease there are as a rule no symptoms, certainly not the classical symptoms of cough, expectoration, blood spitting and loss of weight publicized so frequently. There may be present those less definite symptoms of gastric upset, lack of endurance, fatigue, and so on, but they as a rule do not make sufficient impression on the patient to cause him to seek medical advice. Thus it becomes readily apparent that if we are to find tuberculosis we must direct our efforts to the adult groups, and if we wish to find early disease we must consider some method that will reach such groups in the period before noticeable symptoms have developed.

The logical answer would be a periodic Roentgen ray examination of the entire population. The expense involved in such an approach should not be considered excessive, if we measure our results in lives and community resources saved, for today we have invested many millions of dollars in buildings and equipment to fight tuberculosis, which are costing millions more to maintain, and in the final analysis we are still making rather slow progress in the control of the disease.

It is really not necessary that we should attempt such a wholesale job. Here we have reasonably clear-cut guides. In addition to age and sex incidence we have much data on occupation and economic status of the individual. All of which will assist us in selecting those groups among whom we may expect to find the greatest return.

The mass approach in case finding among apparently healthy individuals is a Roentgen ray job. Fortunately, we have a machine that is well equipped to make large-scale screening operations at a minimum of cost and with a reasonable result. The Powers Rapid Roentgen ray machine has indicated beyond a question of a doubt within the past 5 years that mass action is within our reach. It is well to mention here that this method, or any other similar to it, is but a single step in a well-rounded tuberculosis control program. In any community program the contact case is the most desirable approach and should be the foundation around which these other devices are built.

The first use of this method as a case finding proposition was in New Haven, Conn.,^{3a} by the Department of Health, in 1933. That survey was chiefly confined to High and Junior High School students where 6393 persons were Roentgen rayed in 10½ working days, a speed never before accomplished in such work. Our findings clearly indicated the age incidence factor as of the 12 (0.19%) diagnosed tuberculous, 11 were above 16 years. The percentage diagnosed tuberculous by age periods, including about 200 school teachers were as follows:

Age 11 to 15, 3879 examined, 1 (0.03%).

Age 16 to 20, 1461 examined, 6 (0.41%).

Age 21 to 25, 82 examined, 2 (2.44%).

Age 26 to 30, 74 examined, 2 (2.70%).

The incidence of childhood type lesions for the entire group was 6.01%, and it increased steadily with the higher age groups.

Since this case finding survey was completed there have been numerous others by the same method throughout the country; in all, it is estimated approximately at 300,000 persons. A considerable amount of this work has been done among school children. Unfortunately, there has not been a uniformity of interpretation nor have all these results been reported. Some few of these studies however are of the greatest interest because they clearly illustrate the problems herein discussed.

Following the New Haven survey the Connecticut State Department of Health⁶ undertook a program to offer the Roentgen ray to school children throughout the state during the winter of 1933 to 1934. This work has never been completely analyzed as to age groups; however it was largely among the grades below High School. There were 56,942 Roentgen ray pictures made. They were interpreted by the medical staffs of the State Sanatoria under rigid checking and therefore may be accepted as closely conforming to the National Tuberculosis Association standards. Of the total, 95.5% were considered negative, only 33 (0.06%) were diagnosed as pulmonary tuberculosis, probably active. There was a total of 1936 (3.4%) referred to the family physician for follow-up, the majority of which (773) was considered only as suspicious. This survey cannot be

said to have been a successful case finding adventure, if we are to consider the costs involved and the cases found. The real value of this program was in its educational stimulus in making the school population, and indirectly the lay populace as well as the medical profession, Roentgen ray conscious. This result may or may not be a valid expenditure of funds. There is a growing body of opinion against the indiscriminate use of our resources charged against hypothetical accounts. We have no proof of the yield in our educational measures, and we can with certainty estimate the cost of case finding measures.

During 1933, Barnard¹ utilized the Paper Roentgen ray method in the study of 18,749 individuals on Home Relief in New York City. This was the first mass survey of such a group that we have recorded, and the findings were most illuminating. For the entire group, 2779 (14.8%) were designated for further investigation. There were 2047 (10.9%) diagnosed as tuberculosis. Of the total, 476 (2.5%) were considered definite, 592 (3.2%) suspects, and 979 (5.2%) as healed. In addition there were detected 732 (3.9%) with obvious cardiac lesions. In the latter group, subsequent follow-up confirmed the Roentgen ray diagnosis and showed a close correlation with luetic infection. The persons Roentgen rayed in this study were comparable only in that they were on relief and that Roentgen rays were offered only to those members of families 10 years or older. Two distinct groups were reached, 10,202 from Harlem where there was a predominance of negroes and Porto Ricans, and 8517 from Red Hook-Gowanus, where there was a predominance of whites. The findings generally in the Harlem group were higher. This emphasized the point previously raised that an intelligent selection of adult groups can be made.

There were three general conclusions in this survey of the greatest moment: 1, a routine survey of apparently healthy individuals revealed 2.5% with pulmonary tuberculosis; 2, if the survey had been confined to those 20 years or over all tuberculosis found below that age would have been discovered in the follow-up of contacts; 3, the classification of disease found indicated that over 70% of the lesions were in a minimal stage.

Barnard reports a per capita cost of \$1.78 for the Harlem group, and \$1.22 for the Red Hook-Gowanus, where certain improvements in organization methods were introduced.

Downes² made a further study of the data on the cases Roentgen rayed in the Red Hook-Gowanus District. She presented the data by age, sex and color for important tuberculosis which tended to show definitely the increase in incidence with increasing years and the characteristic differences between sexes as has been commented on previously in this discussion. She also reported on the follow-up of these cases and contacts in the routine clinic examinations. Of the 272 reexamined, 196 (72.1%) were classified as minimal, 28

(10.3%) as moderately advanced and 18 (6.6%) as advanced, 9 (3.3%) were undiagnosed and 21 (7.7%) were reversed from the diagnosis on paper. A study of 73 cases classified as suspects on Paper Roentgen ray were later classified as follows: 16 (21.9%) as minimal tuberculosis, 1 (1.4%) as childhood type, 21 (28.8%) were undiagnosed and the remaining 35 (47.9%) as non-tuberculosis.

There were 543 families with 1873 contacts listed for follow-up. For all ages 64.8% were examined, the highest rate being in 54 families where the primary case was advanced or moderately advanced disease in the primary case, and the lowest in 207 families where the primary case was suspicious or non-tuberculous lesions. The new tuberculosis found by these examinations revealed chiefly minimal lesions, the percentage being about equal for all ages in the families with a primary case of minimal, the suspect and non-tuberculous cases. No cases were diagnosed in contacts in families in which the primary case was moderately or advanced disease. This finding was not explained in the report by Miss Downes. Here again the age incidence factor was clearly substantiated, being lowest under 20 years and reaching its peak or about 26 times greater at 50 years and above.

During 1934, the Department of Health inaugurated another survey of this character in lower Manhattan. It involved 25,170 individuals among which we found 824 (3.3%) with manifest pulmonary tuberculosis; of the 824 cases diagnosed, 89.6% were previously unknown. We designated 2900 individuals for follow-up and found 278 (9.6%) with active tuberculosis.

During 1935 and 1936, another survey of a somewhat similar character was conducted at our Meinhard Health Center among Porto Ricans. In this study, we did not use the Powers Rapid Paper Method, instead we utilized an existing radiographic unit and celluloid films, chiefly because of the limitation of space. The persons invited for Roentgen ray were on Home Relief rolls, predominantly of Porto Rican extraction, and limited to those 15 years or older. A complete analysis of these data is under way which will include the costs involved. There were 3214 persons Roentgen rayed and given a routine chest examination on the first visit, 207 (6.4%) were diagnosed as tuberculous. Of the 207 cases diagnosed adult form tuberculosis, 119 (57.5%) were classified as active. The minimal lesions in this survey represented 83% of the total pulmonary cases.

During the current year we have returned to the Harlem area with an enlarged W. P. A. staff to carry on an intensive combing of the entire area. In this area, our population is predominantly negro and Porto Rican, and the death rates are the highest of any area in the City. The negro population in New York City represents about 5% of the total, yet it is responsible for almost 25% of our annual deaths from tuberculosis. Thus far we have

taken approximately 25,000 Roentgen rays with essentially the same results in new tuberculosis, minimal and cardiac lesions as found in the survey by Barnard in 1933. All 3 of the foregoing studies are now being carefully analyzed and will later be reported in detail.

Our experience in this type of mass survey of apparently healthy persons has been most satisfactory and appears to be the best possible approach to the problem now available. The finding of early lesions permits the maximum results in securing arrest at an early date, and further serves to make more economical use of our limited hospital beds. In the Meinhard study, we arranged with 2 of the City Hospitals to reserve about 12 beds for the immediate hospitalization of cases. These beds were used primarily for the early and doubtful cases where intensive bedside study was desirable to determine activity, and for those suitable for pneumothorax. In the latter group, it was possible to induce their collapse promptly after admission, and within a short period discharge them to ambulant care. This method has proven to be of great value, as it is a source of great encouragement to the patient and represents considerable economy in the use of institutional facilities. All cases of advanced disease in need of longer hospital care were immediately placed in other City Hospitals.

Fellows,⁴ at the Metropolitan Life Insurance Company, has reported results of the greatest significance. He has utilized the fluoroscope to a greater degree of perfection than most workers in this country. By this method in conjunction with the Roentgen ray and careful physical examination he detected 141 previously unknown cases, of which 65% were classified as minimal. The proportion of minimal cases referred to Mt. McGregor, the Metropolitan Sanatorium, were 5 times as great as the average admissions to other sanatoria. The majority of these patients were detected at a time before they had toxic symptoms. The close affiliation with Mt. McGregor resulted in prompt hospitalization and a more rapid arrest of the disease. His experiences clearly indicates what may be done successfully in a large business organization.

Colonel Pillsbury,⁷ at Camp Dix, New Jersey, routinely Roentgen rayed 7405 C. C. C. men, predominantly white and under 30 years. Seventy (0.94%) were classified as active, 76 (1%) were questionably active tuberculous, and 376 (5%) were tuberculous with no activity. Thus he found a total of 522 (7%) with tuberculous lesions of the adult type. The lesions adjudged non-active on this examination, considering the age of the men, should nevertheless be considered as potentially active. His percentages of disease in the groups over 35 years were in each instance higher than in those under 30 years. If these findings are at all indicative of what might be expected among all enrollees in the C. C. C. Camp throughout the country, it may be readily concluded that a similar program should be a part of the Government's responsibility in their administration.

From the standpoint of Government responsibility we should naturally consider the Army, Navy and Marines as well as Civil Service and other employees. If such a device had been available in 1917 at the time of the Draft, the taxpayer today could easily have been relieved of hundreds of millions of expenditure in compensation and hospital costs.

After a careful perusal of the volume of material in the current literature on tuberculosis surveys, it becomes immediately obvious that the great bulk of our effort in the past has been devoted to contact examinations. This is fundamental in any tuberculosis program. The problem among this group that is presented time and again is that as a rule we only examine about half of the known contacts, and that the percentage is highest among the younger ages where we do not expect to find manifest tuberculosis. The adult ages are the most important and demand greater effort to secure cooperation. A study of mortality and morbidity by age groups clearly indicates these facts.

We have always devoted a greater amount of effort to the child rather than the adult. Partly because of the greater ease with which they can be reached and partly because there has been a general feeling that if the early manifestations of tuberculosis could be detected there we could prevent later serious disease in adult life. Since 1920 there has been numbers of extensive surveys among apparently healthy children to determine the incidence of infection and disease. These studies have shown in general an increasing frequency of both as the age periods advance. The incidence of pulmonary tuberculosis has been lower than the childhood types. The yield of pulmonary lesions has been so small that such methods may well be considered excessively costly as case finding methods. The importance of the childhood type lesion is still a debatable issue. If we accept the theory that such lesions are a potential menace then our attitude should be to develop a definite program for their detection and later supervision. On this point there is some information of interest, but much more is required before we can accept it as a sound procedure.

Stewart⁹ reports, from his experience at Lymanhurst in the supervision of 10,000 children, that in only 0.04% had he observed a progression from a childhood to an adult type.

Pope,⁸ reporting on 5000 children followed in the Massachusetts clinics, stated that the progression from childhood to adult type is 0.93%.

Hall and Chang⁵ reported on 1007 Chinese of the professional class. Of 144 originally classified as trachea-bronchial tuberculous lymphadenitis, 6 (4.2%) developed manifest pulmonary tuberculosis in an average of 54.5 months.

Edwards^{3b} reported on 155 individuals with a diagnosis of childhood type from the New Haven Dispensary. In 9 (5.8%) there had been noted a progression to adult pulmonary tuberculosis within

an average period of 242.7 days, all of which occurred during late adolescence.

These reports are significant but require substantially more volume before we can definitely state that the detection of childhood type lesions is a productive source of later adult lesions.

A comparison of our mass studies among apparently healthy children and adults clearly indicates that the latter group is the most productive in significant tuberculosis, or the type that is or will become debilitating and a community problem. It is firmly believed that we have reached the time when we should definitely shift our emphasis from the child to the adult. This shift need not be made blindly as we have a considerable volume of facts and data that clearly indicates the broad general paths that we should follow. From the standpoint of age, 15 years is the lower level, as to sex, our emphasis in females should be greatest between 15 and 30 years, after which we should continue with a consistent drive. In the case of males we again begin at 15 years but find our peak between 50 and 60. From the economic factor we can expect a higher yield in the low income groups and from the tenement house districts. Racially, the colored groups will show higher percentages than the whites in about the same age periods and economic divisions. From the occupational standpoint our course has been clearly defined by Whitney¹⁰ in her analysis of death rates by occupations on the basis of data of the U. S. Census Bureau, 1930. If the tuberculosis administrator will carefully evaluate these various factors in his community it is believed he can intelligently proceed to formulate a sound case-finding program that will be productive in its results and at a cost commensurate with the funds invested.

REFERENCES.

- (1.) Barnard, M. W.: Quart. Bull. Milbank Mem. Fund, 11, 233, 1933. (2.) Downes, J.: Ibid., 12, 134, 1934. (3.) Edwards, H. R.: (a) Trans. 29th Annual Meeting, National Tuberculosis Assn., p. 238, 1933; (b) Am. J. Pub. Health, 25, 941, 1935. (4.) Fellows, H. H.: Am. J. Med. Sci., 188, 533, 1934. (5.) Hall, G. A. M., and Chang, C. P.: Am. Rev. Tuberc., 30, 193, 1934. (6.) Knowlton, M., and Horning, B. G.: Conn. Health Bull., 48, 195, 1934. (7.) Pillsbury, Col. H. C.: Personal Communication, 1936. (8.) Pope, A. S.: J. Am. Med. Assn., 97, 846, 1931. (9.) Stewart, C. A.: Ibid., 100, 1077, 1933. (10.) Whitney, J.: Death Rates by Occupations, National Tuberculosis Assn., June, 1934.

DIAGNOSTIC IMPORTANCE OF THE TONGUE IN INTERNAL MEDICINE.*

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Examine the Tongue! Were the tongue carefully inspected in every patient reporting to the physician or dentist, important diag-

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nostic pointers would frequently be found. Too many clinicians merely order "Stick out your tongue" and 10 seconds later have no idea what they have seen. They have looked but have not seen. In the Chinese language, there are 2 words, one meaning "to look," the other, "to look see;" it is this ability "to look see" which should be developed by physicians.

There are practitioners who unfortunately resort too much to the laboratory method of diagnosis. Examination of the tongue and palpation of the pulse have fallen by the wayside with many young physicians. Gastro-intestinal Roentgen rays, gastric and duodenal analysis, electrocardiographs, orthodiagrams, and the like are often needlessly requested before a thorough history and physical examination of the patient have been completed. This is true, to a lesser extent perhaps, in our hospital wards and outpatient departments. An overzealous but misguided interne, in a mistaken effort to prove his skill before the chief, will drive a tired, weakened patient through the gamut of special tests in the shortest possible time to have the diagnosis the following morning for ward rounds. He may ignore important leads in diagnosis presented by such simple manoeuvres as examination of the scalp and skull for possible metastatic lesions, inspection of the tongue, finger nails, umbilicus, and anus, and palpation of the pulse.

Hippocrates described the tongue as it appears in numerous diseases. Careful routine inspection of this organ reveals manifestations of many systemic diseases. Among these are the chancre, mucous patch, or gumma of syphilis; the strawberry tongue of scarlet fever; the smooth glossy appearance in pernicious anemia and sprue; the pigmentation in Addison's disease; the pallor in severe anemias; the cyanosis in congestive heart failure, congenital heart disease, and polycythemia; the dryness in diabetes mellitus, fevers, mouth breathers, and dehydration; the recurrent canker sores in allergic individuals; the ulcerations of acute leukemia and agranulocytic angina (pernicious leukopenia);^{3,7} the characteristic lesions encountered in drug sensitivity or poisoning; the glossitis of severe anemias of pregnancy, dysentery, simple achlorhydric anemia, and Plummer-Vinson syndrome; the yellow pigmentation most evident along the margins in obstructive jaundice; the tremors of paralysis agitans and hyperthyroidism; the sharp, quick, jerky movements of the tongue in chorea; the scars of epilepsy; these are examples of the importance of the tongue for internal medicine.

The lymph drainage from the tongue is chiefly to the submaxillary and upper and lower deep cervical nodes; the submaxillary nodes receive drainage from the anterior two-thirds of the tongue; the deep cervical nodes, from the posterior third. The motor nerve supply of the tongue is from the twelfth nerve. Since the nucleus of this nerve lies well below that of the facial nerve (seventh),

paralysis of the tongue may occur on the side opposite to that of a concomitant facial palsy. In paralysis of one side of the tongue, this organ when protruded deviates toward the paralyzed side pushed by the non-affected muscles on the healthy side. Ignorance of this relation has led to faulty neurologic diagnosis.

Common sensation for the anterior two-thirds of the tongue is excited through the lingual branch of the fifth nerve, whereas the glossopharyngeal nerve excites common sensation and taste for the posterior third. The sensation of taste for the anterior third is stimulated through the chorda tympani. In diseases involving the epiglottis, one not infrequently encounters reflex cough or hic-cough; this has an anatomic basis, for the epiglottis as well as a small area of the tongue anterior to it is supplied by the internal laryngeal branch of the superior laryngeal nerve.

To evaluate the abnormal tongue, familiarity with the tongue is indispensable, noting particularly color, fur, pallor, papillæ, evidence of inflammatory changes, blood-vessels on the under surface, form, size, movement and humidity. Most textbooks of medicine today devote little space to this organ. The diseases they describe usually include acute, chronic, and Möeller's glossitis, black tongue, leukoplakia, syphilis, tuberculosis, mycoses, and tumors.¹⁶ The tongue may be narrow and pointed at the tip or large and flabby with a thick and rounded tip and with margins marked by the teeth. In nervous individuals, the tongue is quickly protruded and quickly withdrawn. In the phlegmatic, its motions are sluggish. In old age, the tongue is usually coated and less moist than in younger individuals and becomes dry and even glazed at the onset of the slightest ailment. This is of importance lest we regard as serious that which is only a trivial disorder.⁴

Alterations in the appearance of the tongue are commonly related by the lay mind, as well as by many physicians, to disorders of the gastro-intestinal tract. It has been regarded as the mirror of the stomach.¹⁹ Lewis¹⁴ says: "red raw tongue, red raw gut." The time was not far distant when a white tongue was looked upon as a sure sign that the stomach was out of order and that a dose of calomel was indicated.⁵ Many persons have a coated tongue in health, especially smokers.⁴

The coated tongue is the abnormality most frequently encountered. The so-called fur of the tongue is thickened epithelium covering the filiform papillæ plus various bacteria. The filiform papillæ are the most numerous and smallest of the papillæ. Each is a conical projection, sometimes ending in fringes of hairlike processes. The epithelium covering these is constantly shed and worn away and as constantly replaced.⁸

Fitzwilliams⁸ has divided the process of furring of the tongue into several stages: the dotted or stippled tongue, the coated or loaded

tongue, the white strawberry tongue, the furry or shaggy tongue, and the typhoid, dry, brown, crusted tongue. The dotted tongue often occurs with the slightest gastric upset or dietary indiscretion. The strawberry tongue is characteristic of the early stages of scarlet fever, but is also seen in many acute infections, including acute bronchitis, typhoid fever, pneumonia, etc. A diagnosis of scarlet fever should never be made on the appearance of the tongue alone. A coated tongue is frequently seen in association with emotional disturbances in the patient. In intestinal disturbances not complicated by a deranged stomach or dehydration, there is no characteristic change in the tongue; but habitual constipation is often associated with a large, furred tongue. The tongue may be furry in areas which are temporarily out of use, as around chronic ulcers when pain immobilizes this part. A crusted, brown tongue is frequently encountered in intestinal obstruction, peritonitis, terminal cardiac failure or malignancy, etc.

A red, bare or smooth appearance of the tongue may be associated with long standing chronic disorders such as empyema, dysentery, diabetes, tuberculosis, etc. The wearing of an upper plate over long periods of time occasionally produces a smooth, polished, bright red tongue, without pain or inconvenience. Although in many acute disorders of the gastro-intestinal tract the tongue tends to become furred, in acute gastritis it is frequently red, especially at the tip and edges. In acute peritonitis, the tongue is usually small, red, and tender, with little fur and is usually dry.

In carcinoma of the stomach, the tongue may be clean and appear healthy if there be no associated febrile reaction. Schwindt²⁰ has found in many cases of gastric or duodenal ulcer a peculiar change in the tongue manifested as multiple, round or oval, confluent epithelial defects, which disappeared on healing of the ulcers. These looked like superficial ulcers, were not sensitive, and were frequently symmetrical; they were approximately 2 to 8 mm. in size; the edges were smooth. He saw them occasionally with carcinoma of the stomach. In most instances, these lesions were chiefly on the posterior part of the tongue, in the middle, anterior to the large papillæ; occasionally they were unilateral.

Fenwick⁶ noted a definite smell from the tongue itself (not from the breath) with abdominal sepsis. This may be the smell characteristic of pus or rather a fecal odor, sickening to the observer. He has postulated that the tongue may give the first indication of the extremely rapid absorption (in this case of toxic material) from the peritoneum. This smell from the tongue remained even after gargling and washing the mouth. In these cases the tongue usually was not covered by fur, but was dry and beefy.

Discolorations of the tongue may be significant or may be derived from the foodstuffs. Significant changes occur in Addison's disease,

xanthelasma and ecchymoses (as from injury, purpura, or scurvy). In Addison's disease, in addition to the pigmentation elsewhere in the body, there are often bluish-black smears on the mucous membrane of the lips, cheeks and tongue, as if a pen had been wiped upon them. Stains from fruits, acids and alkalis, metals, chocolate, tobacco, nuts, prunes, licorice, etc., may discolor the tongue. The bluish discoloration of the tongue produced by grape juice persists for several hours and can be misleading.

Binkowitz² described in relation to the tongue an early sign of cardiac decompensation. If the tongue is protruded from the mouth and is held in a pendant position for at least a minute, the normal red color gives way to a blue or cyanotic hue, or in severe cases becomes almost black. If the patient elevates the tongue to the back of the upper incisors without exerting pressure a marked distention of the ranine veins occurs, which Binkowitz believes is an early sign of circulatory failure.

Glossitis with atrophy of the lingual papillæ is a common manifestation in pernicious anemia, achlorhydric anemia, the anemia of pregnancy,¹³ pellagra, sprue, Plummer-Vinson syndrome,^{17,21-23} malnutrition attended by dysentery and anemia,¹¹ intestinal stricture, pyloroplasty complicated by peritonitis, dibothriocephalus latius infestation¹⁰ and achlorhydria.¹⁵ Middleton showed that rats placed on a low vitamin B diet present a smooth bald tongue with marked papillary atrophy. He inferred that in most cases an atrophic tongue is dependent on vitamin B deficiency. The completely bald tongue associated with pernicious anemia can exhibit return of papillary markings with liver treatment.

Middleton¹⁹ made tongue prints on smoked paper. His conclusions were as follows: Patients with hyperchlorhydria rarely have smooth tongues, but often scrotal or coated tongues. In organic non-malignant disease of the gastro-intestinal tract there is a tendency to the coated and scrotal types of tongue. This is more marked when hyperchlorhydria coexists and is apparently proportional to the degree of the hyperacidity. Peptic ulcer shows the most evident tendency in this direction, with chronic colitis and chronic cholecystitis following in order. When there is achlorhydria, smoothing of the tongue is common. Functional conditions are rarely attended by smoothing of the tongue. Neither normal nor coated tongues are commonly associated with anemia.

Urticaria may occur locally on the tongue. One such allergic patient could never eat fish without a crop of blisters developing on his tongue.⁸ Lindsay¹⁵ describes a patient in whom canker sores came regularly on the tongue within 24 to 48 hours after eating even the smallest amount of English walnuts. Great swelling of the tongue may develop on an allergic basis; the tongue may also become edematous as a consequence of any inflammatory condition

within the mouth, arising either from a general condition as in mercurial stomatitis, or from local disorder as in ulceration of the gum around a tooth with an infected socket.¹

Among the many causes of "burning tongue" as well as of small ulcerations on this organ is an electrogalvanic burn caused by dentures composed of 2 metals constituting a galvanic battery, the saliva acting as an electrolyte. Lain¹² has pointed out that such galvanic currents may be set up in the mouth generated by 2 metals used in dental fillings, crowns, and bridgework.⁹

An uncommon abnormality of the tongue is the occurrence of a lingual thyroid. In this condition for some unknown reason the anlage of the thyroid gland, which arises in the region of the base of the tongue, fails to migrate or migrates incompletely; 144 proven cases of this condition has been recorded.¹⁸ The symptoms are not characteristic, and arise merely from pressure in this region, resulting in dysphagia, dysphonia and dyspnea. The lesions are usually small, round, hemispherical masses protruding into the pharyngeal fossa. Removal of these masses may produce hypothyroidism. They frequently respond to iodine and thyroid medication.

Other lingual manifestations of systemic disease include uremic stomatitis, disturbances associated with blood dyscrasias, drug eruptions, mycotic infections, neurologic disorders, etc. These will be made the subject of a later report.

Summary. 1. A plea is made for adequate inspection of the tongue of all patients.

2. Some common lingual manifestations of systemic diseases are described.

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REFERENCES.

- (1.) Atlas of Pathological Anatomy of the Tongue: Brit. J. Surg. (supp.), 19, 121, 1931. (2.) Binkowitz, B.: Med. J. and Rec., 137, 426, 1933. (3.) Comroe, B. I.: Ann. Dentistry, 3, 17, 1936. (4.) Davis, J. F.: Penna. Med. J., 4, 128, 1900-01. (5.) Dickinson, W. H.: Lancet, 1, 1428, 1903. (6.) Fenwick, P. C.: Brit. Med. J., 2, 16, 1923. (7.) Fitz Hugh, T., Jr., and Comroe, B. I.: AM. J. MED. SCI., 185, 552, 1933. (8.) Fitzwilliams, D. C. L.: The Tongue and Its Diseases, London, Oxford University Press, 1927. (9.) Hollander, L., Shonfield, L., and Fisher, A.: J. Am. Med. Assn., 100, 1029, 1933. (10.) Isaacs, R., Sturgis, C. C., and Smith, M.: Arch. Int. Med., 42, 313, 1928. (11.) Keefer, C. S., and Yang, C. S.: Nat. Med. J. China, 15, 701, 1929. (12.) Lain, E. S.: Arch. Dermat. and Syph., 25, 21, 1932. (13.) Larrabee, R. C.: AM. J. MED. SCI., 170, 371, 1925. (14.) Lewis, G. E.: Practitioner, 125, 749, 1930. (15.) Lindsay, H. C.: Calif. and West. Med., 33, 729, 1930. (16.) Meakins, J. The Practice of Medicine, St. Louis, The C. V. Mosby Company, 1936. (17.) Moersch, H. J., and Conner, H. M.: Arch. Otolaryng., 4, 112, 1926. (18.) Montgomery, M. L.: Trans. Am. Assn. Study Goiter, p.145, 1935. (19.) Oatway, W. H., and Middleton, W. S.: Arch. Int. Med., 49, 860, 1932. (20.) Schwindt, L. W.: Med. Times and Long Island Med. J., 60, 242, 1932. (21.) Suzman, M. M.: Arch. Int. Med., 51, 1, 1933. (22.) Vinson, P. S.: Minnesota Med., 5, 107, 1922. (23.) Witts, L. J.: Guy's Hosp. Rep., 81, 193, 1931.

LOSS OF BODY HEAT AND DISEASE.

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WITH regard to infectious diseases it is well recognized that the hereditary constitution plays an important rôle in determining whether or not an individual will resist exposure to particular kinds of microorganisms. There are mutations which, apparently in a specific way, confer immunity against particular infections, though the nature of these genetic protective mechanisms is unknown. There are also hereditary traits in body build which affect the chances that an individual will contract certain infections, such as pulmonary tuberculosis. But with regard to organic disease the tendency still prevails to believe in the existence of clear-cut distinctions between hereditary ailments, making their appearance earlier or later in life, and pathologic changes due to influences of the external or internal environment. From experimental studies, however, it is becoming ever clearer that sharp division lines here also do not exist. This is true even for congenital abnormalities. Thus, the incidence of polydactyly in guinea pigs, in addition to its dependence upon the presence of certain genes, appears to be influenced by external agencies acting upon embryonic growth, by litter size, by weight and age of the mother, and probably by still other factors.²⁰ Or, the frequency of appearance of harelip and cleft palate in mice, in addition to genetic factors, has been found to depend upon sex of the individual, litter size, age of the mother, and probably numerous other agencies.¹⁷ There are many instances of a similar nature. This evidence indicates that the actual expression of a trait is likely to be the result of complex interactions. Such interactions may take place (a) between the major genetic determiners of a trait and one or many other genes (genetic environment or residual heredity); (b) between the genes or gene controlled events and physiologic processes within the organism or, before birth, within the mother's body (internal environment); and (c) between hereditary factors or genetically determined structures or functions and the surroundings of the developing or fully formed organism (external environment). Multiple, simultaneous or successive, interrelationships provide an unlimited source of variation. Only a detailed analysis of such interdependence can give a real insight into the etiology of pathologic phenomena.

It is likely that the genesis of many disturbances of structure and function involves a chain of events, with the more important links represented by interactions between the external environment and the organism or its parts, and by internal readjustments in response to changes in particular parts or organs. Observations which illus-

trate relationships of this type have come to light through studies with so-called Frizzle fowl and a short account of this work may serve to call attention to the necessity for clinical observations of a similar nature.

Our work with Frizzle chickens was started with the intention of ascertaining the manner of inheritance of the plumage traits to which this breed owes its name. The characteristic features of the plumage of Frizzle fowl are curling and brittleness of the feathers, and the latter by abrasion frequently leads to more or less complete bareness of the body. It was soon found that these peculiarities are determined by a single gene with incomplete dominance over the normal plumage condition.¹² At the same time it was realized, however, that Frizzle chickens differ in many ways from normal fowl. There is great variability in all of the abnormal traits, but the following features are generally present. The basal metabolism is much increased. At an external temperature of 28° C. (82° F.) the metabolism of Frizzle chickens is above that of normals. Within the range of 28° to 17° C. no changes occur in the metabolic level of normal fowl, but in Frizzle chickens the metabolism increases by about 4% for each degree of reduction in the environmental temperature, and at 17° C. (50° F.) the metabolism of Frizzle chickens exceeds that of normal ones by already more than 100%¹; it continues to rise with falling external temperature. The heart rate of Frizzle fowl is much increased (adult average at room temperature is 27% above normal in females and 68% above normal in males) and is markedly labile.^{2a} There is frequently a distinct sinus irregularity, and sometimes more serious injury to the heart, for example, heart block.³ The heart itself shows conspicuous hypertrophy of both ventricles,^{2b} and this hypertrophy tends to become more pronounced with age.¹³ The amount of circulating blood is definitely increased, especially in mature Frizzle fowl.¹³ There are also changes in the cellular composition of the blood. In Frizzles which live in a relatively favorable external environment the number of red cells and the relative frequency of the different types of white cells are much more variable than in normal chickens, though the averages do not differ significantly. If conditions are less favorable (for instance, low external temperature), we find a definite relative lymphocytosis and leukopenia and subnormal hemoglobin values. The relatively frequent occurrence of immature red cells in the circulating blood of Frizzle chickens indicates more rapid destruction and replacement than is normal.^{11a} The spleen is enlarged. The food intake of Frizzle chickens generally is greater than normal, and, presumably as a direct consequence of this, it is found that the crop, the gizzard, the pancreas, and the kidneys are larger than normal. Length and especially capacity of different parts of the intestinal canal also exceed that of normal fowl. Young Frizzle chickens show a conspicuous lack in body fat, while adult Frizzles

frequently have excessive fat deposits. Water vaporization is reduced to about half the normal amount. Between hatching and the age of sexual maturity the mortality of Frizzle chicks is much greater than normal. Sexual maturity generally is delayed, and may be suppressed entirely if conditions are unfavorable. Size and structure of the sex glands vary greatly. The ovaries tend to be much smaller than normal. The testes of young Frizzle males frequently are considerably larger than normal and show signs of increased sperm production and of exhaustion of the tubules; in sterile Frizzle males past the normal age of sexual maturity the testes generally are very small. It is of interest also that the eggs of Frizzle hens, irrespective of their mates, show reduced hatchability (increased embryonic mortality). Among the glands of internal secretion the thyroids and adrenals are strikingly abnormal. The adrenals as a whole are large in proportion to body weight¹³ and the amount of medullary tissue is increased in comparison with the cortex.¹⁰ Size and structure of the thyroids of Frizzle chickens vary with the conditions of the external environment, ranging from exhaustion atrophy (low external temperature) to hypertrophy and hyperplasia (more favorable environmental temperature) and to normal structure but increased size (protection from low temperature plus high-fat diet).

It seems likely that the organism of Frizzle chickens in many other ways differs structurally and functionally from that of normal fowl. However, let us turn to the question of etiology. How does this complex syndrome arise? The majority of symptoms vary in extent and severity with external conditions. This has been established for basal metabolism, food consumption, disturbances of circulation and of reproduction, and for the findings in the glands of internal secretion. The one constant feature is presented by the plumage changes. The frizzled condition of the feathers is determined within the feather follicles. This is shown not only by the lack of influence of variations in the external environment upon the plumage; but, if a piece of skin of a newly hatched Frizzle chick is transplanted onto a normal feathered host, the transplant will develop typically frizzled feathers in spite of its normal organic surroundings.¹⁰ This suggests strongly that the plumage peculiarities of Frizzle fowl are the only trait under immediate gene control, while the other changes are links in a chain of secondary alterations. We shall refer below to further proof for this conclusion.

The curliness of the feathers unquestionably reduces greatly the heat insulating value of the plumage of Frizzle fowl. This loss of protection becomes exaggerated with abrasion of the feathers and bareness of the body. Hence, it is found that the temperature differential between body and surrounding air is much greater in Frizzle than in normal fowl, and it is not surprising that in a cold environment the body temperature of Frizzle chickens tends to fall below

the normal level. Such symptoms of exposure have been produced in normal feathered chickens by removal of part of the plumage and keeping the birds in a cold environment.^{5,9b}

The abnormalities of Frizzle chickens in many ways bear a striking resemblance to the symptoms of Graves' disease or of experimental hyperthyroidism. Such parallel phenomena concern acceleration of metabolism and of heart rate, hypertrophy of the heart, increase in blood volume, lymphocytosis and leukopenia, reduced hemoglobin, histologic structure of the thyroid, temperature lability, and so on. Even the increased temperature differential between the body surface of Frizzle fowl and the surrounding air has its parallel in frequent increases of the skin temperature in humans suffering from Graves' disease.¹⁴ Are Frizzle chickens, then, in a condition of hyperthyroidism? The fact that water vaporization is reduced, the opposite of what generally happens in hyperthyroidism, already raises some doubts in this respect. Experiments which were designed to test this question revealed that environmental conditions must be taken into account. Various physiologic tests demonstrate that at low external temperature, with basal metabolism at peak values, Frizzle chickens are subnormal with regard to the amounts of circulating thyroid hormone. This is shown by the following facts. Greater than normal amounts of desiccated thyroid must be administered to Frizzle chickens in order to produce molting (the typical sign of hyperthyroidism in fowl) and loss of body weight.¹ The Reid Hunt test is negative.^{11b} Subnormal body temperature will become normal when thyroid hormone is supplied.^{9a} In view of all available observations, this can mean only that, in spite of increased thyroid activity (as evidenced by the histologic structure of the gland), the body is not supplied with sufficient amounts of hormone to satisfy the demands created by the accelerated metabolic rate. On the other hand, if Frizzle chickens are suddenly transferred from cold to warm surroundings, it is found that they pass through a short period of hyperthyroidism (increase of body temperature; positive Reid Hunt test; disturbances of feather pigmentation, etc.). If Frizzle chickens remain permanently at very high temperature, they appear to be physiologically normal.

Frizzle fowl show the most extreme abnormalities when they are brought up in a relatively cold environment. Since under such conditions these birds have less thyroid hormone circulating in their body than normal chickens, their abnormalities must be due directly to heat loss, sympathetic overstimulation and increased metabolic rate. This is interesting with regard to such features as the hypertrophy of the heart. In the case of Graves' disease it has been contended by some that the hypertrophy of the heart is preceded by myocardial damage and by specific effects of the thyroid hormone upon the heart muscle,⁷ while others assumed that the hypertrophy

is simply the result of increased work. Our observations on Frizzle fowl clearly favor the latter alternative, *i. e.*, overwork, since hyperthyroidism is excluded as a possible cause and other direct effects on the heart tissue appear unlikely. If, in addition to increased work, excitatory effects play a rôle in the heart hypertrophy, they must be assumed to originate from increased metabolism or peripheral sources (heat loss in Frizzles) rather than from the thyroid.

The outstanding rôle which environmental temperature plays with regard to all our observations on Frizzle fowl is explained by its importance in relation to loss of body heat. The greater is the heat loss, the higher is the basal metabolism. Other adaptations and readjustments follow. But under extreme conditions (that is, extreme for Frizzle fowl) various organs, *e. g.*, the heart or the thyroid, may reach their limits of adaptability, with consequent exhaustion and structural break-down or functional disturbances, leading to death. If heat loss stops suddenly (transfer to heated quarters), less thyroid hormone is needed for metabolic activity, but since the thyroid gland needs some time to adjust itself by reducing its output to the new physiologic level, there ensues a short period of oversupply of hormone with consequent symptoms of hyperthyroidism. *Mutatis mutandis*, the same may be assumed to hold with regard to the adrenals.

Direct proof for the correctness of this interpretation was obtained when the regulation of body temperature of Frizzle fowl was compared with that of normal chickens from which a large part of the plumage had been removed.³⁶ Both types of birds showed exactly the same reactions. In a cold environment their body temperature was somewhat below the normal level. At low external temperature the injection of adrenalin or ephedrine caused an abrupt decline of body temperature and death in Frizzle and partly depummed normal chickens, while only a slight effect was observed in the control animals. In a warm environment, on the other hand, similar treatment produced little effect in Frizzle and partly depummed normal chickens, while in the controls it caused hyperthermia and death. Ergotamin gave similar results. These observations show that typical symptoms of Frizzle fowl can be duplicated by removing a part of the body insulation from normal chickens, thereby exposing them to excessive loss of body heat. The results suggest also that the sympathetic nervous system acts as a transmitter of the stimulation caused by the abnormal heat loss and the accelerated metabolism. In rats it has also been shown recently that the effects of thyroid hormone administration vary with the environmental temperature; in fact, within a certain temperature range (and for a uniform dosage) it was found that the relation of external temperature to survival period of the animals was approximately linear.⁴

If Frizzle fowl had been studied without regard to their "clothing"

and without consideration of the conditions of their living quarters, their abnormalities almost certainly would have been diagnosed as due to endocrine disturbances. This leads one to wonder if scanty body protection and lack of proper heating or other climatic factors do not play a much greater rôle in the etiology of human disease than is realized at present. For Frizzle fowl we are certainly justified in saying that with regard to structure and function their bodies are "resonators" of their environment. We have no reason to doubt that the scanty feathering of Frizzle chickens only exaggerates a situation which exists in normal fowl. Does not this evidence suggest that there is truth in Petersen's claim¹⁶ that humans are "cosmic resonators," and that cosmic changes are likely to be reflected in manifold ways by the human organism? These problems deserve intensive study.

Among human diseases it was pointed out by Mills^{15a,b} that the incidence and severity of exophthalmic goiter, diabetes and pernicious anemia appear to be related to storm frequency and temperature variability. More or less convincing evidence of a similar nature was put forward by Petersen for many other pathologic phenomena.¹⁶ A condition which probably has much in common with the findings in Frizzle fowl is the "glycosuria of vagrants" reported by Hoppe-Seyler.⁶ This author observed glycosuria of short duration, together with circulatory and digestive disturbances, as a consequence of an irregular and poorly balanced diet if linked with physical exertion and exposure to inclement weather. In general, the rôle which exposure to low external temperature plays in human metabolism^{15,16,18} essentially is the same as was observed in Frizzle fowl and may be assumed to lead to similar consequences.

Exposure to cold is recognized as a partial cause in paroxysmal hemoglobinuria, Thomsen's disease and Raynaud's disease.¹⁹ While in these cases low temperature only precipitates the symptoms which have their real cause in internal abnormalities, they demonstrate that an organism which functions normally at one external temperature, may show serious disturbances at another. There are further similarities, however, between these conditions and the situation in Frizzle fowl. In Raynaud's disease, for instance, abnormalities of the sympathetic nervous system apparently lead to endocrine and metabolic disturbances similar to those produced in Frizzle chickens by sympathetic overstimulation. These endocrine and metabolic abnormalities in both cases are symptoms rather than causative agencies. Evidence is accumulating that the same holds true in other diseases, even in the case of such a classical "thyroid" disturbance as Graves' disease.

Decision of what is cause and what effect is frequently made difficult on account of reciprocal relationships. Thus, increased secretion of thyroid hormone accelerates metabolism but acceleration of metabolism (for instance, by lowering of external tempera-

ture) also stimulates secretion of thyroid hormone. Similar reciprocal relations exist between thyroid and adrenal⁸ and probably in still other cases where the autonomic nervous system acts as an intermediary.

Our observations on Frizzle chickens also emphasize the conclusion that the histologic picture of increased activity of the thyroid gland or, in fact, the demonstration that the thyroids produce more hormone than normal does not necessarily indicate that the organism as a whole is in a condition of hyperthyroidism. The opposite, *i. e.*, hypothyroidism, may be, and in the case of Frizzle chickens actually is found. This will always occur when the demands of the body for thyroid hormone on account of increased metabolism, adrenal insufficiency or for other reasons exceed the capacity of the thyroids for hormone production.

The complexity of events produced by the Frizzle mutation is interesting in still other respects. We have seen that all the different changes represent a series of adjustments to a single primary factor, namely, increased loss of body heat. The plumage abnormality which accounts for the excessive heat loss may in turn trace back to a metabolic disturbance. Histologic study of the feather follicles has so far produced little evidence for structural abnormalities in feather formation, and it seems likely that the frizzling is due to disturbances in keratin metabolism. In many other instances where changes in several organs or functions are found, we may similarly be dealing with complex adaptations and readjustments rather than with multiple disease symptoms *sensu stricto*. Organisms are delicately balanced. Changes in one function necessitate adjustments in other functions. If an organism is unable to make such adjustments, it will perish. This unquestionably happens in many Frizzle chicks (increased mortality between hatching and maturity), and the same may be assumed to occur in other instances of complex syndromes. The immediate cause of death may be only failure of adjustment or of compensation in one organ to alterations in the functioning of another organ. Latitude of adaptability of various organs rather than their perfect adjustment for one "normal" level of activity will frequently hold the balance of life and death. Among Frizzle chickens, for instance, those which from birth on have larger and better functioning thyroids, undoubtedly will have a greater chance to survive, and it has actually been found that, apparently due to natural selection, the thyroids of Frizzle chicks at hatching are larger than those of other breeds of fowl and show increased activity.¹⁰ Yet, frequently they cannot keep pace with the demands of the body. In some other respects the adjustments of Frizzle chickens appear to be more successful.

On the whole, the evidence from Frizzle fowl demonstrates impressively the inseparableness of organism and environment. As function and structure are only aspects of one entity, so is each

organism in multiple ways an expression of its particular environment. It seems certain that this applies to humans also. But in our society the effects of the natural environment are likely to be complicated by social factors which are another real and integral part of our existence. The fact, however, that the human environment is more complex than that of lower animals does not make it less likely that our bodies reflect its forces.

REFERENCES.

- (1.) Benedict, F. G., Landauer, W., and Fox, E. L.: The Physiology of Normal and Frizzle Fowl, with Special Reference to the Basal Metabolism, Storrs Agri. Exp. Sta. Bull. 177, 1932. (2.) Boas, E. P., and Landauer, W.: (a) *Am. J. Med. Sci.*, 185, 654, 1933; (b) *Ibid.*, 188, 359, 1934. (3.) Boas, E. P., and Schwartz, S. P.: *Med. Rec.*, 143, 50, 1936. (4.) Bodansky, M., Pilcher, J. F., and Duff, V. B.: *J. Exp. Med.*, 63, 523, 1936. (5.) Giaja, J., and Gelineo, S.: *Arch. intern. d. Physiol.*, 37, 20, 1933. (6.) Hoppe-Seyler, G.: *München. Med. Wehnschr.*, 47, 531, 1900. (7.) Hurxthal, L. M.: *Am. Heart J.*, 4, 103, 1928-1929. (8.) Katzenelbogen, S.: *Intern. Clin.*, 3, Ser. 44, 73, 1934. (9.) Landauer, W.: (a) *Arch. intern. de Pharmacod.*, 49, 130, 1934; (b) *Ibid.*, 56, 121, 1937. (10.) Landauer, W., and Aberle, S. D.: *Am. J. Anat.*, 57, 99, 1935. (11.) Landauer, W., and David, L. T.: (a) *Folia haematol.*, 50, 1, 1933; (b) *Arch. intern. de Pharmacod.*, 49, 125, 1934. (12.) Landauer, W., and Dunn, L. C.: *J. Heredity*, 21, 291, 1930. (13.) Landauer, W., and Upham, E.: *Weight and Size of Organs in Frizzle Fowl. A Study Concerning Organ Adjustments Following Excessive Loss of Body Heat and Accelerated Metabolism*, Storrs Agri. Exp. Sta. Bull. 210, 1936. (14.) Laroche, G., Saidman, J., and de Zuloaga: *Compt. rend. Soc. de Biol.*, 122, 10, 1936. (15.) Mills, C. A.: (a) *Endocrinology*, 16, 52, 1932; (b) *Living with the Weather*, New York, Caxton Press, 1934. (16.) Petersen, W. F.: *The Patient and the Weather*, vols. 1 and 2, Ann Arbor, Edwards Brothers, Inc., 1934-1936. (17.) Reed, S. C.: *Genetics*, 21, 339, 1936. (18.) Schade, H.: *Wärme. Handb. d. normalen u. patholog. Physiol.*, 17, 392, Berlin, Julius Springer, 1926. (19.) Sunder-Plassmann, P., and Müller, K.: *Klin. Wehnschr.*, 30, 152, 1937. (20.) Wright, S.: *Genetics*, 19, 506, 1934.

THE CALCIUM ION CONCENTRATION OF THE SERUM IN ALLERGIC DISEASES.*

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THE belief that calcium may be a factor in allergy is based on the studies of the physiologic effects of inorganic salts by Ringer, Howell and others,¹ which showed that calcium salts lessened the permeability of membranes and depressed smooth muscle. Since transudation of serum and smooth muscle spasm play important

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parts in allergic phenomena, calcium compounds have frequently been advised as therapeutic agents in these diseases.¹²

Some writers have found an actual calcium deficiency associated with allergic conditions, but the results of various authorities are quite contradictory. Novak and Hollander,¹¹ Brown and Hunter,² and Sterling¹⁷ have reported that the serum calcium is low in allergic diseases. On the other hand, Schwartz and Levin,¹⁵ Crip and McElroy,⁵ Ramirez,¹³ Kern and Teller⁹ reported normal figures, while Schamberg and Brown,¹⁴ Sonnenschein and Pearlman,¹⁶ Greenbaum⁷ and Drillhon⁶ all found values higher than normal. The discrepancies may in some cases be due to choice of the normal range, but it is obviously impossible to reconcile all these opinions.

Furthermore, it is important to consider the state of chemical combination of the calcium in the serum, which was poorly understood when most of these papers were written. It is now known that a part of the calcium is freely diffusible through semipermeable membranes, while the remainder is bound to the serum protein and is not diffusible. There is some difference of opinion as to the subdivision of the diffusible fraction, but probably most of it is present as simple calcium ions, while a small portion is combined with citrate and other complex anions.

Only the ionized portion of the calcium is physiologically active. Variations in the non-diffusible portion, which accompany differences in the serum proteins, do not cause the characteristic symptoms associated with changes in the serum calcium. Several methods have been suggested for determining the diffusible calcium: (1) by dialysis or ultrafiltration through suitable membranes; (2) by considering the cerebrospinal fluid a protein-free filtrate of the plasma; (3) by electrometric measurements with a calcium electrode.

Greenberg and Gunther⁸ applied the ultrafiltration method to the sera of 14 allergic patients and found the diffusible calcium to be normal in all but one case. Cantarow⁴ by analyzing the spinal fluid of allergic individuals found an increase of the filtrable fraction with a normal total serum calcium. Brown and Ramsdell,³ in experimental anaphylaxis, found the diffusible calcium definitely elevated. However, none of these methods of fractionating the calcium has proved really practical or accurate.

During the past few years, McLean and Hastings¹⁰ have developed an entirely different method which gives promise of greatly advancing knowledge of this matter. Variations of the calcium ion in fluids perfused through an isolated frog heart produce characteristic effects on the contractility. By this means it is possible to measure quite accurately the amount of ionized calcium in serum or other suitable fluids. Furthermore, they were able to show that the calcium ion concentration so determined bore a mathematical relationship to the total serum calcium and the serum protein, as measured by ordinary analytical methods. Therefore, by carrying

out these two chemical procedures and applying their formula or diagram, it is possible to calculate the ionized calcium without resorting to the complicated physiologic method.

Method. This method of study was applied to the sera of 53 patients with various allergic diseases, and 25 control observations were made upon relatively normal subjects. Both groups were free of other diseases known to affect calcium or nitrogen metabolism. Blood for analysis was drawn by means of a tourniquet, but prolonged stasis was avoided. In a preliminary study, it was found that the error introduced by careful use of the tourniquet was relatively small, approximately $-.04$ mg. of ionized calcium per 100 cc., and since it affected the normal and allergic figures equally, this method was suitable for practical use.

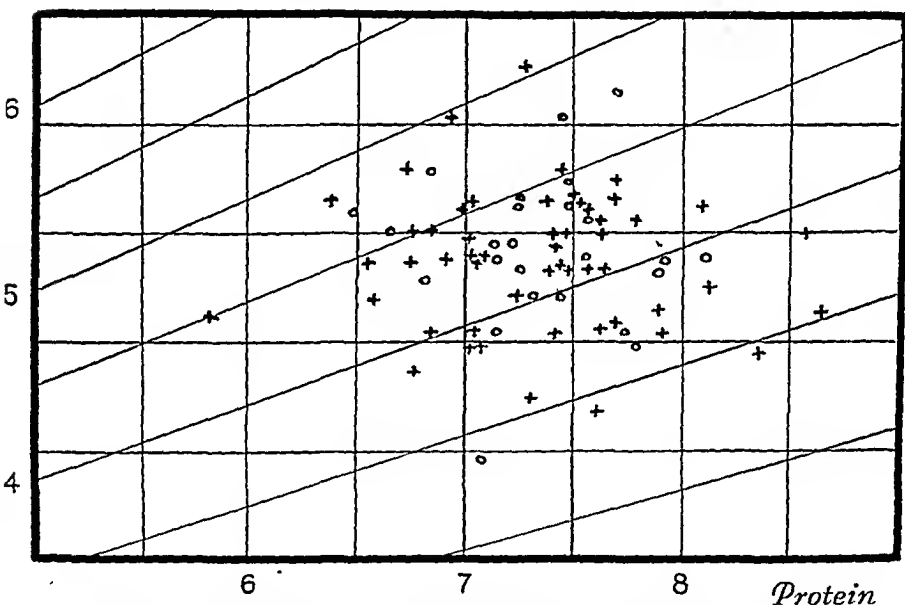


CHART I.—The distribution of calcium values for allergic and normal sera.

Each cross represents an allergic serum, each circle a normal serum. The horizontal lines represent total calcium in mg. per 100 cc., the vertical lines protein in grams per 100 cc. The oblique lines represent the ionized calcium (after McLean and Hastings). If a point is located by determining the total calcium and protein, the ionized calcium is readily estimated from the diagram.

The total calcium was determined by the Tisdall¹⁹ method, using 2 cc. of serum. To check the accuracy of the determination, 3 or 4 analyses were made on each of 6 different sera. The average deviation of a single analysis was $\pm .35$ mg. per 100 cc. In the beginning of the work, a number of determinations were done on 1 cc. samples of serum, but the results were considerably higher and more variable than when a 2 cc. sample was used, so they are not included in the final series.

The total nitrogen was determined by the Kjeldahl method, and the protein nitrogen obtained by subtracting .133, a correction for non-protein nitrogen and blank based on the average of 52 sera studied by Stull, Glidden and Loveless¹⁸ in this laboratory. The error introduced by this step is negligible, since none of the patients included in the series had kidney

disease. The protein determinations could be reproduced with a greater precision than the calcium figures; the average deviation of analyses on a single serum was $\pm .05$ gm. per 100 cc.

Results. Of the 25 normal sera, 21 showed total calciums between 9 and 11 mg. per 100 cc., the usually accepted limits of normal. Two were high and two low, the highest 11.29 and the lowest 7.88. The distribution of the allergic group was essentially the same, 45 of 53 cases falling between 9 and 11 mg., 7 being low (minimum 8.35) and 2 high (maximum 11.52).

When the ionized calcium was calculated, the distribution of cases in the normal and allergic groups was again very similar. Of the 25 normals, 19 were between 3.7 and 4.7, with the highest 4.8 and the lowest 3.3. Among the 53 allergies, 44 fell between 3.7 and 4.7, the highest was 5.0 and the lowest 3.4.

TABLE 1.—CALCIUM VALUES FOR ALLERGIC AND NORMAL SERA.

	Cases.	Total calcium.	Ionized calcium.
Normals	25	9.80 \pm .08	4.20 \pm .05
All allergies	53	9.74 \pm .06	4.20 \pm .04
Asthma	31	9.80 \pm .09	4.19 \pm .04
Hay fever	11	9.52	3.99
Urticaria	5	10.12	4.52
Eczema	4	9.40	4.30
Migraine	2	9.64	4.35

The averages for the two groups are shown in the table. For the total calcium the normal average was 9.80 mg. per 100 cc. with a probable error of $\pm .08$, the average of the allergic group $9.74 \pm .06$. The difference was well within the limits of error. The average ionized calcium of the normal group was $4.20 \pm .05$, that of the allergic patients $4.20 \pm .04$.

The values for the different allergic diseases are also tabulated. The asthmatic group of 31 cases had an average total calcium of 9.80 and an ionized calcium of 4.19. When the asthmatic group was subdivided into purely allergic, infective and mixed cases, the values of each class were nearly the same.

The other four groups, hay fever 11 cases, urticaria 5 cases, eczema 4 cases and allergic (skin-sensitive) migraine 2 cases, all gave figures well within the normal limits and as near the normal average as could be expected with such small numbers of cases. One serum taken during a moderately severe constitutional reaction, following an injection of cottonseed extract, showed a total calcium of 10.35, ionized fraction 4.4.

We feel that if calcium deficiency were a physiologic factor in the occurrence of allergic symptoms, its presence could be demonstrated best by the study of the calcium ion concentration of the serum, since it is the calcium ion that is actually thought to affect permeability and smooth muscle contraction. The method of McLean and Hastings seems especially suitable since it is ultimately based on the

physiologic action on the frog heart, which probably parallels the effects on other tissues. We therefore consider our results evidence against the importance of calcium deficiency as a factor in allergic reactions.

It is of course possible that calcium compounds might show some therapeutic benefit, even though there was no actual deficiency, just as the injection of adrenalin relieves an asthmatic although his body is presumably producing a normal amount of this hormone. We are not prepared to express an opinion on this phase of the problem. We have treated a few cases of persistent asthma with large doses of calcium chloride by mouth and a few with viosterol. Great care was taken to choose cases whose condition was static, and no other change in therapy was made at the same time. One patient improved greatly while receiving calcium chloride, without measurable change in the serum calcium. None of the other cases showed definite benefit.

Summary. The calcium ion concentration in the sera of patients with various allergic diseases showed no significant variation from the normal value. The same was true of the total serum calcium.

REFERENCES.

- (1.) Bayliss, W. M.: Principles of General Physiology, 3d ed., London, Longmans, Green & Co., 1920.
- (2.) Brown, G. T., and Hunter, O. B.: Ann. Clin. Med., 4, 299, 1925.
- (3.) Brown, H., and Ramsdell, S. G.: J. Exp. Med., 49, 705, 1929.
- (4.) Cantarow, A.: Calcium Metabolism and Calcium Therapy, 2d ed., Philadelphia, Lea & Febiger, 1933; AM. J. MED. SCI., 179, 497, 1930.
- (5.) Crieep, L. H., and McElroy, W. S.: Arch. Int. Med., 42, 865, 1928.
- (6.) Drillhon, A.: Compt. rend. Soc. d. biol., 115, 23, 1934.
- (7.) Greenbaum, S. S.: Arch. Dermat. and Syph., 16, 553, 1927.
- (8.) Greenberg, D. M., and Gunther, L.: Arch. Int. Med., 46, 72, 1930.
- (9.) Kern, R. A., and Teller, I.: J. Allergy, 2, 488, 1931.
- (10.) McLean, F. C., and Hastings, A. B.: AM. J. MED. SCI., 189, 601, 1935.
- (11.) Novak, F. J., and Hollander, A. R.: J. Am. Med. Assn., 81, 2003, 1923; 84, 534, 1925.
- (12.) Pottenger, F. M.: AM. J. MED. SCI., 167, 203, 1924.
- (13.) Ramirez, M.: J. Allergy, 1, 283, 1930.
- (14.) Schamberg, J. F., and Brown, H.: Arch. Dermat. and Syph., 9, 368, 1924.
- (15.) Schwartz, H. J., and Levin, O. I. Ibid., 10, 544, 1924.
- (16.) Sonnenschein, R., and Pearlman, S. J.: J. Am. Med. Assn., 83, 1973, 1924.
- (17.) Sterling, A.: J. Lab. and Clin. Med., 13, 997, 1928.
- (18.) Stull, A., Glidden, M., and Loveless, M.: J. Allergy, 7, 333, 1936.
- (19.) Tisdall, F. F.: J. Biol. Chem., 56, 439, 1923.

A SURVEY OF UNDULANT FEVER AND BANG'S DISEASE IN THE UNITED STATES.

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IN 1887, Bruce² isolated the causative agent of undulant fever, which he named *Micrococcus melitensis*. Other workers revealed that it was, in reality, a rod form and not a coccus, and accordingly

it became known as *Bacillus melitensis*, and also as *Bacterium melitensis*. The term *Brucella* (named after the discoverer), is now usually employed and infections by species of this genus are known today as brucelliasis and brucellosis.

In 1897, Bang,¹ of Copenhagen, isolated a small bacterium, the *Bacillus abortus*, from the uterine discharges of cows which had aborted. Bovine infectious abortion is frequently designated as Bang's disease. In 1918, the classic work of Miss Alice Evans,⁴ brought together the two diseases—Malta fever in man, and infectious abortion in cattle. In 1924, Kecer⁶ reported a definite case of human infection with *Bacillus* (now known as *Brucella*) *abortus*. Carpenter,³ and others, later succeeded in isolating the latter organism from the blood and various lesions of many patients.

The infectious abortion of swine, caused by the porcine strain, *Brucella suis*, is also pathogenic for both man and cattle. In districts where hog raising is carried on, it is recognized that this animal and the porcine strain, may be the source and cause of human infections.

The results of the numerous investigations during recent years have led workers to the following conclusion: brucellosis in man and animals is a widespread disease in this and other countries throughout the world. Though some workers regard the causative agent of infectious abortion in cattle and that of undulant fever in man as very similar, with serologic distinctions as the only difference, others regard the relationship as still an open question. In man, the bovine caprine (from goats) and porcine types of brucellosis have been found. In this country, the caprine type is relatively infrequent. It is known that in some regions sheep are infected, and it is possible that a distinct ovine strain of brucella exists. Recently horses have also been proven to be sources of infection.

Infected raw milk or its products, direct contact with the flesh or discharges from infected animals (either diseased or carriers), and improperly cooked meat from such animals are, in the light of our present day knowledge, the principal source of the infection in man.

The possibility of untreated water, contaminated with the urine or discharges (or even with raw milk) of affected animals or carriers, and even insect vectors serving as a source of the spread of brucellosis, must be kept in mind.

It is impossible to estimate the extent of brucellosis in man and in cattle, as exact statistical records are not available. Furthermore, it is known that the vast majority of cases that occur in man remain unrecognized. The same disease has been confused with other diseases. In many instances, due to the mildness of the infection, an exact diagnosis is not made; and in other instances, for any of several reasons, known cases of undulant fever may not have been reported to the health authorities.

In preparing for a plan of investigation, to be reported at a later date by one of the authors, a thorough statistical study of the prevalence and mortality of undulant fever was deemed advisable. Such a study,* together with a survey of the distribution and prevalence of Bang's disease, was initiated with the hope that it might bring to light data of significance in a more comprehensive understanding of human brucellosis.

The results of a questionnaire sent to several European countries are given in Table 1.

TABLE 1.—UNDULANT FEVER IN EUROPEAN COUNTRIES (1930-1935).

Country.	Year.					
	1930.	1931.	1932.	1933.	1934.	1935.
England . . .	30	42	65	62	52	39
France . . .	*	*	293	392	424	*
Germany . . .	626†	520†	498†	483†	530†	513†
Italy . . .	1156	1454	1997	1923	2896	2750
Netherlands . .	18	23	21	27	34	25

* No report.

† October 1 (previous year) to September 30 (inclusive).

The information in Table 2 was obtained in response to a questionnaire sent to the Health Department in each state. Our data includes only those cases actually reported to the health authorities. A number of the states included the number of reported cases of undulant fever for the year 1935. Of the 21 states making this report, 13 showed an increase over 1934, the remaining 8 states showed a decrease in 1935. The total number of cases referred to hereafter, includes those in all states in the United States, excepting South Dakota from which state information was not available.

Our survey showed a total of 9317 cases of undulant fever reported in the United States for the years 1928 to 1934 inclusive. Comparison of the incidence in several European countries with that in the United States is shown in Table 3.

The figures shown under "Mortality Rate for Undulant Fever" in Table 4, were obtained from the number of cases, as reported by the individual states, and the number of deaths, as reported by the United States Census Bureau.

Discussion. Analysis revealed many interesting facts, some of which have been reported previously by various workers. The following are also of interest:

One would expect to find some correlation between the number of infected herds revealing Bang's disease, or at least the percentage

* This presentation has been made possible only by the excellent coöperation of the many individuals and organizations who have so kindly assisted us in the accumulation of this data. We are greatly indebted to the United States Bureau of the Census, to the Bureau of Animal Industry and the Bureau of Entomology and Plant Quarantine of the United States Department of Agriculture, and to the Health Departments of the individual states throughout the country for the assistance they have rendered. We are also indebted to the officials in the several foreign countries who have forwarded to us the data included in this report.

TABLE 2.—REPORTED CASES OF UNDULANT FEVER (BY INDIVIDUAL STATES)
(1928-1934).

States.	1928.	1929.	1930.	1931.	1932.	1933.	1934.	Total 1928- 1934.
Alabama	17	23	20	17	12	45	134
Arizona . . .	6	12	21	12	10	27	18	106
Arkansas . . .	*	*	*	2	1	10	10	23
California . .	11	73	120	106	109	136	158	713
Colorado . . .	1	5	2	7	5	4	7	31
Connecticut .	4	12	21	20	33	36	55	181
Delaware . . .	*	1	7	2	2	6	10	28
Florida	8	4	3	2	5	9	31
Georgia . . .	10	14	10	8	35	39	63	179
Idaho . . .	*	*	*	*	*	51	3	54
Illinois . . .	1	39	63	124	72	94	101	494
Indiana	35	27	30	17	18	127
Iowa . . .	118	174	145	48	85	151	187	908
Kansas . . .	14	85	99	64	79	86	99	526
Kentucky . .	11	13	8	20	7	8	8	75
Louisiana . .	2	17	20	59	35	28	54	215
Maine . . .	8	8	10	5	16	27	27	101
Maryland . .	11	18	32	47	49	39	49	245
Massachusetts	*	*	6	15	15	11	15	62
Michigan . .	8	4	14	19	45	81	101	272
Minnesota . .	12	42	62	72	62	72	102	424
Mississippi	11	13	3	27
Missouri . .	*	50	135	162	179	79	54	659
Montana . .	2	3	4	4	11	16	15	55
Nebraska	1	..	4	1	..	4	10
Nevada	2	1	3
New Hamp- shire	1	4	9	9	23
New Jersey .	A	A	14	49	36	28	27	154
New Mexico .	1	2	2	5	3	7	5	25
New York . .	B	106 B	157	171	223	255	301	1213
North Carolina	C	C	C	C	4	15	19	38
North Dakota .	5	5	10	42	1	4	5	72
Ohio . . .	11	29	84	118	84	56	66	448
Oklahoma	4	2	13	5	15	4	43
Oregon . . .	13 D	19	24	24	22	25	34	161
Pennsylvania .	3	25	35	33	47	54	80	277
Rhode Island .	..	3	2	..	1	11	9	26
South Carolina	2	17	4	2	5	2	20	52
South Dakota .	*	*	*	*	*	*	*	*
Tennessee . .	2	2	11	7	10	12	4	48
Texas	3	5	11	31	43	21	114
Utah . . .	1	3	2	8	7	11	33	65
Vermont . . .	2 E	4 E	19	16	13	14	25	93
Virginia . . .	3	4	25	20	37	46	33	168
Washington . .	*	22	26	34	18	24	25	149
West Virginia .	*	*	1	..	1	2	2	6
Wisconsin . .	8	42	83	71	59	104	86	453
Wyoming	2	2	2	..	6

Total in the

U. S. . . 270 890 1349 1475 1523 1787 2023 9317

* (Data not available or not given)

.. (No cases reported)

A (Reportable beginning July, 1930)

B (Reportable beginning July, 1929)

C (Reportable beginning 1932)

D (July to December)

E (Actual records commence in 1930)

of positive reactors among the cattle of the infected herds in a state, and the corresponding number of cases of undulant fever in that same state. These statistics do not necessarily reveal this information. Let us, for example, analyze the following two groups of states. One we will designate as the "High Morbidity Rate,"

TABLE 3.—REPORTED UNDULANT FEVER CASES IN EUROPEAN COUNTRIES AND THE UNITED STATES.

Country.	Years.	Total number of reported cases.
England	1926-1935	318
France	1932-1934	1,109
Germany*	1930-1935	3,170
Italy	1924-1935	18,086
Netherlands	1930-1935	148
United States	1928-1934	9,317

* October 1 (previous year) to September 30 (inclusive).

which will consist of those states in which the rate is in excess of 15 cases per 100,000 population; the other group, the "Low Morbidity Rate," will include those states with a rate less than 2 cases per 100,000 population.

High morbidity rate.			Low morbidity rate.		
State.	No. of cases.	Rate.	State.	No. of cases.	Rate.
1 Wisconsin	453	15 2	Arkansas	23	1 2
2 Minnesota	424	16 5	Mississippi	27	1 3
3 Missouri	659	18 2	Tennessee	48	1 8
4 Kansas	526	28 0	Oklahoma	43	1 8
5 Iowa	908	36 7	Massachusetts	62	1 5
6 Arizona	106	24 3	N. Carolina	38	1 2
7 Oregon	161	16 9	W. Virginia	6	0 3
8 Vermont	93	25 9			

The following reveals the percentage of herds containing infection, and the percentage of reactors among the cattle of the infected herds of the previously mentioned states.

State.	Percent- age of infected herds.	Percent- age of reactors.	State.	Percent- age of infected herds.	Percent- age of reactors
1 Wisconsin	31 1	19 3	Arkansas	15 1	15 2
2 Minnesota	38 0	17 8	Mississippi	60 4	9 0
3 Missouri	31 9	18 1	Tennessee	65 2	12 7
4 Kansas	57 6	19 9	Oklahoma	48 7	13 4
5 Iowa	57 9	22 0	Massachusetts	51 3	15 6
6 Arizona	28 2	10 6	N. Carolina	35 0	11 0
7 Oregon	18 4	14 8	W. Virginia	9 8	16 9
8 Vermont	49 3	15 2			
Average	39 05	17 2		40 8	13 4

From these last two tables we learn that there was a high percentage of infected herds in those states showing a low morbidity rate for undulant fever, though the percentage of reactors was somewhat less, yet not proportional to the existent morbidity rate of undulant fever cases. Attempted correlation of data from other

TABLE 4.—INCIDENCE, MORBIDITY AND MORTALITY OF UNDULANT FEVER, AND DATA CONCERNING BANG'S DISEASE IN THE UNITED STATES.

Registration area.	Population 1930.	Cases reported		Deaths reported 1928-1934.	Mortality rate *	Herds tested.	Total No. of cattle tested.	Herds containing infection.	% of herds containing infection.	Total No. of cattle in infected herds.	Number of reactors.	% of reactors in number of cattle tested.*	% of reactors in total number of cattle tested.*
		1928-1934.	1934.										
Alabama	2,645,297	134	5.0	10	7.5	4,333	313,651	2,874	66.3	237,804	23,244	9.0	7.4
Arizona	433,833	106	24.3	3	2.8	1,855	36,038	523	28.2	20,033	2,121	10.6	5.9
Arkansas	5,672,009	713	12.6	5	21.7	20,927	238,922	4,327	15.1	100,227	15,260	15.2	6.4
California	1,035,043	31	3.0	16	3.2	128	8,121	61	47.7	5,119	523	10.2	6.4
Connecticut	1,604,711	181	11.3	2	1.1	409	20,889	201	40.1	15,191	1,518	10.0	7.3
Delaware	238,380	28	11.7	1	3.6	1,381	25,447	332	54.3	11,887	1,631	13.7	8.3
Florida	1,466,625	31	2.1	4	12.9	9,586	236,311	508	36.8	11,689	2,031	17.4	8.0
Georgia	2,902,443	170	6.2	7	13.0	3,837	138,290	1,792	46.5	90,757	9,573	10.6	9.6
Illinois	445,837	54	12.0	4	13.0	1,381	25,447	332	54.3	11,887	1,631	13.7	8.3
Indiana	7,607,084	494	6.5	7	13.0	3,837	138,290	1,792	46.5	90,757	9,573	10.6	9.6
Iowa	3,225,800	127	3.9	18	3.6	14,908	242,856	6,765	32.4	138,088	13,498	14.5	6.9
Kentucky	2,467,900	908	36.7	16	12.6	14,908	242,856	6,765	32.4	138,088	13,498	14.5	6.9
Louisiana	1,879,946	526	28.0	25	2.8	14,900	271,100	9,341	39.4	160,763	28,240	20.1	11.5
Maine	2,034,006	75	2.8	20	3.8	6,462	178,298	3,724	57.9	130,632	25,904	19.9	13.4
Maryland	797,423	215	10.3	10	13.3	28,064	300,915	7,184	25.6	127,478	22,774	17.9	14.6
Massachusetts	1,620,321	101	12.6	16	7.4	5,062	147,590	1,960	38.9	106,610	13,640	12.8	9.2
Michigan	4,253,646	62	1.5	3	3.0	3,211	48,447	1,138	35.4	23,487	4,209	17.9	8.6
Minnesota	4,812,280	272	5.6	0	6.3	26,691	318,838	1,40	31.3	103,724	21,433	20.7	7.8
Mississippi	2,366,445	424	17.3	4	11.1	68,042	1,050,314	2,803	23.3	4,974	776	15.6	9.0
Montana	2,007,979	27	1.3	3	3.0	47,874	135,918	3,203	60.4	508,099	90,254	17.8	6.7
Nebraska	3,620,901	630	18.2	20	1.8	7,699	602,420	15,288	31.9	112,372	10,130	9.0	8.5
Nevada	536,332	10	7.2	1	4.0	5,736	174,480	2,238	29.1	270,970	49,130	18.1	7.5
New Hampshire	90,891	3	3.3	4	3.3	103,258	34,520	2,206	38.5	94,100	14,555	15.5	8.3
New Jersey (A)	4,653,293	23	4.9	1	3.3	33,343	824	824	43.5	57,369	9,795	17.1	9.3
New York (B)	4,028,027	154	3.8	1	1.4	7,962	174,058	501	60.1	40,685	2,640	5.3	8.7
North Carolina (C)	12,619,503	1213	9.6	4	16.0	834	37,818	824	43.5	57,369	9,795	17.1	9.3
Ohio	3,170,287	38	1.2	24	2.0	6,962	174,058	501	60.1	40,685	2,640	5.3	8.7
Oklahoma	682,448	72	10.6	13	34.2	7,397	128,185	1,882	23.7	118,432	11,361	9.6	4.6
Oregon	6,680,837	448	6.7	1	1.4	7,397	128,185	1,882	23.7	118,432	11,361	9.6	4.6
Pennsylvania	9,526,691	161	1.8	7	16.3	37,878	432,961	11,786	31.1	43,972	8,870	21.2	6.3
Rhode Island	9,640,802	277	2.9	4	2.5	31,292	719,525	15,226	48.7	496,403	39,120	23.0	7.3
South Carolina	687,232	26	3.8	5	3.8	609,933	9,985	18.4	261.479	38,774	16.9	6.4	9.2
South Dakota (D)	1,732,567	52	3.0	2	3.8	379,338	5,580	22.0	135.197	22,903	13.4	6.0	10.0
Tennessee	2,608,759	48	1.8	3	3.8	93,094	1,085	39	60.9	1,726	240	13.9	6.0
Texas	5,821,272	114	2.0	6	12.3	18,282	1,085	39	60.9	1,726	240	13.9	6.0
Vermont	302,582	65	13.0	9	7.9	234,593	8,044	65.2	44.964	4,705	10.5	5.1	12.8
Virginia	359,611	93	25.9	1	1.5	366,526	4,462	50.0	187.231	23,747	18.2	10.1	10.5
Washington	2,419,471	168	6.9	10	1.1	114,486	3,096	19.6	263.456	38,576	14.6	10.5	6.5
West Virginia	1,561,967	149	9.5	3	3.9	32,121	621,736	490	49.3	47,431	7,482	15.8	8.9
Wisconsin	1,728,510	6	0.3	1	16.7	381,315	9,345	49.3	181.739	23,668	13.0	8.9	8.8
Wyoming	2,980,282	453	15.2	11	2.4	1,673,107	2,806	9.8	42.472	31,316	18.5	3.7	7.5
Totals and averages	122,309,618	9317	8.7	374	7.9	11,858,859	238,541	38.4	5,936,719	941,383	14.9	8.0	8.0

† (See explanation under text)
 (A) Cases not reported until July 1, 1930, no deaths reported for 1928-1929.
 (B) Cases not reported until July 1, 1930, no deaths reported for 1928-1929.
 (C) Cases not reported until July 1, 1930, no deaths reported for 1928-1929.
 (D) Data on cases not available, 1 death reported in 1933.
 † Calculated by author.

remarks upon the admirable management, cleanliness and cheer of the home, adding that he had never "seen a more model institution," and that the British might do well to emulate its good points in their more numerous establishments. This comment of 1882 has not changed much in tone even in the most recent report on convalescent institutions in Great Britain by Gardiner, 1935, who likewise emphasizes our great dearth of institutions, but our superior equipment and management.

In 1908, Arinstrong¹ drew attention to the fact that 44% of the 31,334 patients discharged from Bellevue were not fit to work, and that 30% were in need of further treatment. In 1915, the Winifred Masterson Burke Relief Foundation, with a legacy of several million dollars, was opened for the purpose of providing free care to the convalescents of New York. It had 300 beds, a receiving office in the city, and special bus transportation. In 1916, Frederic Brush contributed an important paper on "Convalescence in the United States." He felt it unnecessary to review the history of British convalescent homes, because he believed that this country would develop its own type. However, it is interesting to know that as early as 1610, such a house was opened in Bath, Somersetshire, England, to remedy the crowding of the city of Bath with sick poor. In fact, the need for convalescent hospitals in general, is always found to be largely based upon the lack of accommodation for acute cases in the hospitals, necessitating early discharge to make room for new cases, and upon the poor housing conditions of the working class which constitute a real menace to the weak, freshly recovered patient with risk of relapse and chronic invalidization. The better class can easily be accommodated in the more expensive, privately conducted institutions.

With an annual discharge of some 40,000 to 70,000 patients needing convalescent care from the hospitals of New York City alone, it is evident that not even so admirable an institution as the Burke Relief Foundation, accommodating 10,000 patients annually, can cope with this situation. Increasing incidence and of mortality from chronic diseases indicate the crying need for expansion in this field. For this reason, Brush has suggested a plan for central government supervision on a nation wide scale. The New York Medical Center has provided a clearing house, giving daily information as to available beds in convalescent homes. A National Directory of Convalescent Houses has been issued, as well as a directory for convalescent homes serving New York City.

Although the population of the United States is 2.7 times as great as that of Great Britain, and the United States covers an area 33.5 times as large as Great Britain, we have only 179 convalescent homes (1935) as compared with 431 in Great Britain, or 7.1 beds per 100,000 population as compared with 53.6 beds per 100,000 in Great Britain. These figures are taken from Gardiner's book, in

which attention is also called to the fact that in 24 of our states we have no institutions for convalescence whatsoever. Both in Great Britain and Russia the trade unions have contributed their part in establishing convalescent homes for their members. In Russia, where the trade unions play a dominant part in control of the government, Houses of Rest, where adequate convalescent care may be obtained, are maintained not only inside and outside of every city, but also in the various seashore and country summer resorts. Medical treatment, regulated diet and rest, hydrotherapy and means of recreation are provided. The requirements for admission are the same as those demanded in sanatoria. Here in the United States a number of the larger industrial corporations maintain rest homes for their employees. The Philadelphia Electric Company maintains a house in Maryland, where its employees may board for a period of 2 weeks at a very small charge, until they regain their strength. It has accommodations for from 12 to 18 guests.

Needless to say that in this country where until most recently the whole problem has been grossly neglected, provision for special sections of the population, such as the colored people, for instance, has been almost entirely ignored.

According to Bryant, however, the interest aroused in the subject has given impetus to plans on an unprecedented scale, and with our great wealth and greater advances in occupational and dietetic management, there can be no doubt that within a few years our convalescent institutions should lead the world.

Occupational Therapy. Occupational therapy was recognized as a most important adjunct in the treatment of the convalescent sick even in the days of the early Egyptians (2000 B.C.). In 172 A.D. Galen wrote, "Employment is Nature's best physician and is essential to human happiness."

Benjamin Rush emphasized the importance of occupational therapy and recreation in restoration of health. He provided facilities for sewing and embroidery for his women patients, and for farming, carpentry and shoe repairing for his men patients. It was not until 1906, however, that the first school for occupational therapy was opened (Boston) and in 1914, a course in that branch was opened at Teachers' College, New York. In Philadelphia there is the School for Occupational Therapy. There are departments of occupational therapy in nearly all our large hospitals, and this branch of treatment is rapidly becoming recognized as of prime importance in building up and restoring health to convalescent patients.

Government Supervision in England. In England, the types of organizations responsible for the management of its convalescent homes are varied: 82.4% of the institutions in that country are still supported by private philanthropy, including religious groups, social

agencies, charitable trusts and employers, hospitals and voluntary committees. Most of the homes run by the hospitals for their own patients were small, only 7 of 84 containing more than 50 beds.

An effective form of government supervision is made by the Ministry of Health in the form of grants to local authorities and to voluntary committees. According to Gardiner, these grants have been made "to agencies providing care for many different stages of illness, including some convalescent homes. As a method of supervision the giving of grants has been effective because: 1, the plan is carefully worked out by the voluntary committee and the local authority before it is presented to the Ministry; 2, the acceptance of the plan gives the Ministry the right (a) to inspect the institution, (b) to audit the account, and (c) to diminish or discontinue the grant for non-fulfillment of the agreement. This is ample safeguard to the standards of physical care, given if, as in Great Britain, the central authority has a high standard. Through the National Health Insurance Fund central government money goes to the convalescent homes in two ways, namely: (a) as per capita payments from approved societies, both mutual and industrial, coming under the heading of additional benefits, but often listed with other fees in annual reports of voluntary agencies; and (b) grants of lump sums to reserve accommodations for members, or to encourage homes to continue. It is important to remember in this connection that the British plan is both contributory and compulsory; therefore, two-thirds of the money dispensed under this Act had been previously paid by the worker and the employer to the government. Only approximately one-third of the money expended under the National Health Insurance Acts can be called public money in the sense of taxpayers' money."

A few years ago a Committee of the New York Academy of Medicine took up the question of convalescent care and suggested certain standards that should be maintained. The requirements were published by the Welfare Council of New York City under the title of "Minimum Standards for Convalescent Homes," and were used by several institutions in the neighborhood of Philadelphia.

Basis for Estimation of Required Number of Community Beds. A careful survey of the Philadelphia Hospitals was made in 1929 by Dr. Haven Emerson.⁴ In the chapter devoted to convalescent facilities, he states that, "In determining the number of beds which should be provided for institutional convalescent care for patients, who have gone through the critical hazards of acute illness, it is the practice to estimate that such cases will equal 10% of all patients receiving hospital care with 2% additional to provide for patients in need of such services attending out-patient department clinics. On this basis, Philadelphia, with 200,000 patients annually, would have approximately 24,000 patients needing convalescent care each year. At the rate of 17 patients per bed during the year, each

patient having 3 weeks of care, there are required to meet this need, about 1400 beds." Actually, the total number of beds now available is less than 650, a large percentage being in the state of New Jersey.

Ten years ago, under the auspices of the Council of Social Agencies of the Philadelphia Welfare Federation, a special study of facilities for institutional care was made. It was shown that only 27% of 2083 patients needing this care received this service; of the 1523 not served, 1410 did not receive the care because of lack of beds. In a census taken in December, 1928, and January, 1929, in 48 hospitals for patients with acute illness, 426 out of 6030 patients (7%) were classed as convalescent. In other words, in every acute ward, there were a few individuals, who should have been sent from the hospital, and who needed only a quiet, restful regime, such as could be obtained in a convalescent home at one-third to one-half the cost; and a patient's discharge from a hospital leaves available one more bed for an acutely ill patient. According to Dr. Emerson the *per capita per diem* cost of convalescent care has ranged in the past from \$1.75 to \$2.25, depending on the size of the Home. The cost is increased if the paid personnel is relatively large. One employee to 5 patients is generally found adequate, in Dr. Emerson's view. From the attached table, p. 691, this does not seem to be the case.

Convalescent Care in the Philadelphia Area. Although New York City stands first in the care of its convalescents, there are in and around Philadelphia a number of institutions for this purpose. As a very good example, the Dunwoody Home for Convalescent Men at Newtown Square, Pennsylvania, may be cited. It was established through the generosity of the late William Hood Dunwoody, and opened in 1924 on a farm of 122 acres, a short distance from Philadelphia, with a capacity of 45 beds. The buildings are of fireproof construction, and it is said that if finances will permit, end pavilions will be added, increasing the number to 60 beds. All of the bedrooms have a southern exposure.

While certain duties are required of the guests, much emphasis is placed on opportunity for rest and diversion. There are rooms for shuffle-board, pool, billiards and ping-pong. The craze for miniature golf which swept the country a few years ago suggested the establishment of a course at Dunwoody. This has proved an ideal form of recreation for the guests, being most suitable for cardiac patients. Teams are formed, adding the zest of competition. Milk contributes much to the health of the patients and likewise to their gain in weight; in some institutions it has been considered too expensive. At this Home, where inspected raw Ayrshire milk is given freely in the diet, it was found that the gain in weight was most striking.

Another outstanding institution is the Children's Heart Hospital at Bala—in the country, on the edge of the city. The Philadelphia

TABLE 1.—CONVALESCENT HOMES IN THE PHILADELPHIA AREA.

	Beds	Personnel	Weekly charge	Waiting list	Average stay (weeks)	Cost per capita per day	Occupational therapy	Nurses	Physician	Type of patients*					Remarks
										Women (white)	Men (white)	Children (white)	Children (colored)	Women (colored)	
Convalescent Hospital, Broomall, Pa.	31	9	\$5 to \$20	At times	3-4	\$2 50	++	+	Visiting	Yes	.	Girls over 10 years	Occupational therapy highly regarded. Occupat. ther. may be started this fall.
Dunwoody Home, Newtown Square, Pa.	45	17	No charge unless able to pay	Yes	3-4	2 37	-	+	Visiting	..	+	Boys over 18 years	
Ivy Croft Farm, Wayne, Pa.	16	5	Nothing up to \$10 pay	No except in summer	3	2 67	++	+	Visiting	..	+	Occupational therapy helps to pay for itself.
Willow Crest Convalescent Home, Willow Grove, Pa.	80	30	About 50% free \$7-21	Yes	3	1 86	+	+	Visiting	+	+	+	
James C. Smith Memorial Home, Oakbourne, Pa.	22	5	Free	In summer	2	1 80	+	+	Visiting	+ over 21 years	Cost of maintaining home for 1936, \$11,419.63. Number of patient days 6345; average \$1.80.
Cinnamon Home, Riverton, N. J.	27 cribs 3	4	Admission \$2 mother and baby \$3	At times	2	Not given; cost per meal 7c.	+	+	Visiting	+	..	Babies	
Mercer Memorial (Sumner Home, Atlantic City, N. J.)	134	33	\$5 to \$7	Yes	2-5	1 67	-	++	Visiting	++	No waiting, last 2 years. Many inquiries for care of chronic cases. One attendant to 10 children.
St. Francis Country Home, Darby, Pa.	50	5	Free	No	2 or more	Less than \$2	-	++	Visiting staff	
Children's Heart Hospital, Bala, Pa.	50	16	\$3 Med. care	Yes	9 mos.	1 95	Given schooling	+	Visiting staff	+	+	..	Reduction in number of cases of bone and joint tuberculosis. Increase of cardiac cases.
Children's Seashore House, Atlantic City, N. J.	All year 145	56 In summer 30 extra	\$5 (if able to pay)	..	Several months	1 19 to 1 37	Given schooling	+	Physician in charge	+	..	+	+	..	
Convalescent Hospital for Colored Women, 1304 Catharine Street, Philadelphia	25	6	\$7 (\$20 private room)	Often	4	1 75 to 2 05	+	+	Visiting	+	
Richard Home, Devon, Pa.	72	Not in operation													

* There are no convalescent beds for colored men.

Heart Association sponsors it for the care of cardiac children. While there are 75 beds, at present only 50 children are being cared for, owing to lack of finances. The children admitted are under close observation and rest for a prolonged time.

A modern convalescent Home is Willow Crest, under the auspices of the Federation of Jewish Charities. Here an experiment is being conducted in the long term care of children with mild forms of rheumatic infection, with the view of preventing development of serious cardiac disease in later life.



FIG. 1.—“The Dunwoody Home,” Newtown Square, Pa.

At Atlantic City, New Jersey, may be mentioned the Mercer Memorial House for Woman, as Philadelphia is the source of the majority of its patients.

There is a great opportunity awaiting the Magee Memorial Hospital for Convalescents. Anna J. Magee in her will (1917) endowed this institution, the object of which is to relieve the general hospitals of Philadelphia from the burden of support of patients who have passed through the active stages of acute illness. The Hospital is to be governed by a Board of 12 trustees, each hospital having the right to elect a member. Children under 14 are excluded. The trustees have decided to accumulate this fund until they have sufficient money to put up buildings, leaving a sufficient fund for endowment.

The Supplee Fund is another welcome aid to convalescent homes in the Philadelphia area. This insurance fund of \$200,000 is administered by the Board of City Trusts. Any patient in a Philadelphia hospital (except the Philadelphia General) who needs further care is eligible. The board bill at an existing convalescent home is paid by the Board of City Trusts, the maximum allowance being \$20 per week, and the maximum time of care 4 weeks.

The facilities for convalescent care would be increased if physicians could become *convalescent-conscious*—if the phrase may be coined.

Inquiry brings out the fact that there has been almost no advance in the number of available convalescent beds in the past 7 years; in fact, two Homes have fewer beds. One, listed in 1929 as having 35 beds, has only 27 beds today, and another dropped from 35 to 30 beds.

The Babies' Hospital of Philadelphia used to maintain a country branch at Llanerch, which was open in the summer; but unfortunately has been unable to support it for the past 2 years. The authorities hope that they may have funds available to re-open the Home this coming summer.

In spite of the large colored population, there is absolutely no provision for the care of colored men; and the only convalescent hospital for colored women in Philadelphia is one of 25 beds, with a waiting list at all times. This hospital is receiving some State aid.

Inquiry at the various homes reveals the fact that several have a waiting list. In one year, recently, the number of applicants at Willow Crest was 3000, while with its 80 beds only 886 patients could be cared for annually. It is feared that this comment will be further confirmed when the results of the contemplated survey by the Committee of the Council of Social Agencies of Philadelphia are published.

Central Bureau. A great step in advance would be the establishment of a central bureau in the city for the distribution of patients needing convalescent care. According to the Executive Secretary of the Public Health Committee of the New York Academy of Medicine, Dr. Lewinski-Corwin, "Such a bureau would greatly facilitate the work of placing patients and would obviate the need of making inquiries at each individual institution. Such a clearing house would in time become an important factor in the situation by the accumulation of facts concerning available facilities and the character of the work performed at the different institutions. It would serve also in securing better utilization of the Convalescent Homes than is the case at the present time."

Summary. The present paper is a plea for an increase in the facilities for convalescent care. Much would be gained if the situation were realized by administrative and professional staffs and boards of trustees of hospitals, and the ends desired could be accomplished through meetings and conferences arranged by a committee of the Hospital Association. It is certainly hoped that the interest of public spirited philanthropists may be aroused by medical organizations, hospital staffs and physicians in general.

REFERENCES.

- (1.) Armstrong, S. T.: New York Med. J., 87, 437, 1908.
- (2.) Bryant, J.: Convalescence, White Plains, N. Y., Burke Foundation, 1927.
- (3.) Corwin, E. H. L., and Kidner, Mr.: Standards for Convalescent Homes, New York, Burke Foundation, 1930.
- (4.) Emerson, H., Pincus, S., and Phillips, A. C.: Philadelphia Hospital and Health Survey, 1929, Philadelphia, Welfare Federation of Philadelphia.
- (5.) Gardiner, E. G.: Convalescent Care in Great Britain, Chicago, University of Chicago Press, 1935.

CAUSATIVE FACTORS IN THE PRODUCTION OF LAENNEC'S CIRRHOSIS WITH SPECIAL REFERENCE TO SYPHILIS.

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SYPHILITIC cirrhosis is characterized by conspicuous, fibrous scars often associated with gummata and usually accompanied by considerable deformity of the organ (*hepar lobatum*). Diffuse nodular cirrhosis (Laennec's cirrhosis) with none of the usual characters of syphilitic cirrhosis has been repeatedly found in association with syphilitic infection.

The clinical association of cirrhosis of the liver with syphilis was noted in a paper by Pearce⁹ on the Wassermann reaction published shortly after this test was discovered. He collected from the reports of several investigators a large series of cases in which the Wassermann test had been performed. In this series, cirrhosis, of which the type was usually not specified, occurred 30 times, and in 22 of these cases the Wassermann reaction was positive. Hawkins,³ on the contrary, stated that atrophic cirrhosis had no direct etiologic relationship to syphilis.

In 1917, Symmers¹¹ found among the cases of clinically diagnosed atrophic nodular cirrhosis in the wards at Bellevue Hospital 80% with positive Wassermann reactions. Of the cases confirmed at autopsy, 28% were in syphilitic subjects. Wooley¹⁵ reported 3 cases of "hypertrophic" cirrhosis, in 2 of which there was definite evidence of and in 1 the probability of syphilis. In all 3 there was a probability of alcoholism.

In 1200 autopsies studied by Owen⁸ there were 19 cases of nodular cirrhosis of the liver and 3 cases of characteristic syphilitic cirrhosis. In 12 of the 19 cases with nodular cirrhosis the Wassermann test had been done, and it was positive in 5 instances. When the cases with no Wassermann tests were included, the incidence of positive syphilis (5 cases with positive Wassermans and 2 clinically proven cases) was still 37%. There was a history of alcoholism in 6 of the 19 cases of nodular cirrhosis. Both alcoholism and syphilis were present in 4 cases.

Rolleston and McNee¹⁰ believe that congenital syphilis in children may make the liver susceptible to diffuse cirrhosis. They state that occasionally the liver of a child with stigmata of congenital syphilis shows "ordinary" (portal) cirrhosis, distinguishable from the intercellular fibrosis of infants suffering from congenital syphilis. The liver remains vulnerable to subsequent injury so that conditions tending to produce diffuse nodular cirrhosis will more readily produce this change. In other words, congenital syphilis so prepares the soil that cirrhosis may supervene.

In reviewing 2285 autopsies, LeDuc⁵ found 101 cases of cirrhosis which he classified as follows: (1) Atrophic cirrhosis (58 cases or 2.5%); (2) "early cirrhosis which generally had the characters suggestive of early atrophic or early syphilitic cirrhosis" (16 cases); (3) syphilitic cirrhosis (19 cases); (4) "Glissonian cirrhosis" (8 cases). Histologic lesions of syphilis in other organs of the body were found in 60.3% of the cases of atrophic cirrhosis (34 out of 58), and in 66.6% of the cases of atrophic cirrhosis and "early cirrhosis" combined (49 out of 74). When all four varieties of cirrhosis were added together, the incidence of histologic evidence of syphilis was found to be 71.2% (72 cases out of 101). LeDuc suggests that the infrequency of atrophic cirrhosis or Laennec's cirrhosis and syphilis found by other observers may be partly explained by the relative infrequency with which they diagnose visceral syphilis.

Present Study. This is based on clinical and autopsy records of the New York Hospital. In 1977 consecutive cases that came to autopsy, cirrhosis of the liver (all types) was found in 74 instances. The type of cirrhosis was determined by the gross characters of the lesion and by examination of microscopic sections. The results of this analysis are seen in the following table:

TABLE 1.—CLASSIFICATION OF TYPES OF CIRRHOSIS AT NEW YORK HOSPITAL.

	Number.	Per cent.
All cases of cirrhosis	74	
1. Diffuse cirrhosis	45	60.8
A. Nodular (Laennec)	44	
B. Smooth hypertrophic (Hanot)	1	
2. Syphilitic (hepar lobatum)	2	2.7
3. Obstructive	8	10.8
4. Cirrhosis with primary tumor of the liver	7	9.5
5. Central cirrhosis with cardiac disease	2	2.7
6. Miscellaneous	10	13.5
A. Hemachromatosis	3	
B. Cirrhosis with toxic necrosis	2	
C. Splenic anemia	3	
D. Non-lipoid histiocytosis	1	
E. Fibrosis with tuberculosis	1	

Of the 74 cases of cirrhosis, 45 (60.8%) were found to be diffuse, 44 falling into the category of nodular or Laennec's cirrhosis (known also as atrophic or portal), and 1 of smooth hypertrophic cirrhosis, fitting the type described by Hanot. Chief interest centered upon these, but the incidence of syphilis and of alcoholism in the entire group was determined.

There were 2 cases of hepar lobatum or syphilitic cirrhosis with definite clinical evidence of syphilis. In one there was no excessive use of alcohol, and in the other the habits in relation to alcohol were unknown. In the latter the histologic examination of the liver showed, in addition to the deep, puckered, cicatricial lesions, a diffusely distributed cirrhosis.

In almost all of the cases of diffuse cirrhosis in which syphilis

was discovered, this disease was incidental and some other condition for which the patient entered the hospital was apparently more significant. In some instances, there was sufficient evidence at hand to prove conclusively the diagnosis of syphilis (history of chancre, 4+ Wassermann, history of treatment, etc.). There were, however, a number of cases in which, from analysis of the records, syphilis could only be classified as "probable," "possible," or "doubtful." Furthermore, there were a few cases which were classified as "unknown" because the patient had entered the hospital moribund, and the past history and serologic tests were omitted. In the figures showing the incidence of syphilis, cases regarded as "possible" or "doubtful" were not included, though the actual presence of syphilis in some of these is not unlikely.

The single case of Hanot's cirrhosis included in the series was definitely associated with syphilis. This individual also used alcohol to marked excess (Autopsy 6402).

Evidence of syphilis obtained from the data found in the history, physical examination, laboratory tests, and postmortem examination of each case is given below:*

Clinical Abstracts. 1. Autopsy 6352. Male, white, aged 39. History of chancre 20 years before admission and of treatment (amount and duration not known). His wife had a miscarriage at 3 months and no other pregnancy. Blood and spinal fluid Wassermann were negative. Examination of the spinal fluid showed 15 lymphocytes per cm.

2. Autopsy 6402. Male, white, aged 50. Blood Wassermann was 2+ with both alcohol and cholesterol antigens. Ascitic fluid Wassermann was 3+ with alcoholic antigen and 4+ with cholesterol antigen.

3. Autopsy 6425. Male, white, aged 74. Patient had a definite history of syphilis 25 years before death and was treated for 2 years.

4. Autopsy 6911. Male, colored, aged 57, had a sore on the penis "some years ago." Blood Wassermann was 4+ with both antigens. Patient had Argyll-Robertson pupils. Spinal fluid showed 30 cells per cm. of which 80% were lymphocytes. Syphilitic aortitis and aortic valvular disease were found at autopsy.

5. Autopsy 6949. Male, white, aged 36, contracted syphilis 12 years prior to admission and received 5 injections of arsphenamine. Blood Wassermann was 4+ with the cholesterol antigen, negative with the alcoholic antigen. Syphilitic aortitis was found at autopsy.

6. Autopsy 7265. Male, white, aged 49. Luetic infection occurred 10 years prior to admission, and there was "some treatment" at that time. The blood Wassermann was negative. The Kline test was 1+.

7. Autopsy 7229. Male, white, aged 47. Blood and spinal fluid Wassermanns were 4+ with both antigens. Syphilitic aortitis was found at autopsy.

8. Autopsy 7301. Male, white, aged 48. Initial lesion was contracted 12 years before death. Three years later the Wassermann was 4+. This became negative 6 years before death. Patient was treated for 4 years. At his last admission the blood Wassermann was anticomplementary and the Kline test was 1+.

9. Autopsy 7522. Male, white, aged 57, had a chancre in his youth. Blood Wassermann was 4+ with both antigens. Autopsy revealed syphilitic aortitis and an aortic aneurysm.

* Cases 1 to 11 were classified as definite syphilis, Cases 12 and 13 as probable, but inconclusive. Possible and doubtful cases of syphilis were not included.

10. Autopsy 7534. Male, white, aged 56, whose wife had 6 miscarriages, and two children died shortly after birth. Blood Wassermann was 4+ with both antigens.

11. Autopsy 8091. Male, white, aged 53, whose wife had 4 miscarriages (possibly induced). The blood Wassermann was 4+.

12. Autopsy 6250. Male, white, aged 56, whose wife had a possible miscarriage. Patient had failing vision for 3 years prior to admission. Blood Wassermann was 2+ with both antigens. Pupils reacted poorly to light and were small.

13. Autopsy 6275. Male, white, aged 57. Blood Wassermann was 4+ with the cholesterol antigen, but negative with the alcoholic antigen.

All of the 13 cases of diffuse cirrhosis with syphilis were in adults. A case of probable syphilis in a boy of 15 is not included in the list of cases of syphilis with diffuse cirrhosis. This child had advanced diffuse cirrhosis of the type of Laennec. The diagnosis of syphilis did not appear on the hospital chart, and the Wassermann reaction was negative, but irregular teeth, scars over the shins, absent pupillary reflexes, and syphilis in the father indicate that the child had suffered from congenital syphilis. The case recalls the contention of Rolleston and McNee that congenital syphilis increases susceptibility to the ordinary form of nodular cirrhosis.

In the 11 cases of cirrhosis classified as miscellaneous (Table 1), 1 case of hemachromatosis had both syphilis and a history of excessive use of alcohol. The liver in this case showed advanced diffuse cirrhosis.

The incidence of syphilis in the various types of cirrhosis is shown in the following table:

TABLE 2.—INCIDENCE OF SYPHILIS IN CASES OF CIRRHOSIS.

Type of cirrhosis.	No	Syphilis					None.
		Definite.	Probable.	Possible.	Doubtful.	Unknown.	
Diffuse . . .	45	11	2	2	2	1	27
Syphilitic . .	2	2					
Obstructive . .	8			1			7
With tumor . .	7	1		1		1	4
Central . . .	2				1		1
Miscellaneous	10	1			1		8
Total . . .	74	15	2	4	4	2	47

Increase of the interstitial tissue of the liver was experimentally produced by repeated administration of small quantities of phosphorus by Afrecht (1879), Ackermann (1880), Kronig (1887), and Dinkler (1887)⁷. Whipple and Sperry¹⁴ produced hyaline necrosis in the central portions of the liver lobules by repeated chloroforming of animals. Mertens (1896), according to Opie, produced cirrhosis in rabbits by daily subcutaneous injections of small quantities of chloroform dissolved in liquid paraffin. Cirrhosis of the liver was produced experimentally also by injecting certain types of bacteria into the circulation of animals (Hektoen,⁴ Ogata,⁶ and others).

Experiments of Opie⁷ showed that bacterial infection could influ-

ence and even determine the development of cirrhosis in the liver when the latter was subjected to the injurious effects of a toxic agent such as chloroform. He showed that combined infection with the colon bacillus and intoxication by chloroform produced advanced diffuse cirrhosis. The experimental production of cirrhosis had been inconstant when the infectious or toxic agent was used alone.

Villaret, Benard, and Blum¹³ stated that the combination of syphilis and alcohol was responsible for the majority of cases of cirrhosis of the Laennec and Hanot type. They regarded this view as therapeutically important and cited clinical cures in which syphilis had been eliminated before irreparable lesions had become established. In a discussion of the etiologic factors involved in the production of "venous" cirrhosis of the liver, the same authors¹² draw the following conclusions: (1) Alcoholism produces changes in the liver which lower its resistance and allow the localization of a chronic infection; (2) syphilis cannot itself produce "venous" cirrhosis; (3) syphilis produces changes in the portal areas making them more susceptible to the action of alcohol.

Cade¹ concluded that syphilitic infection was frequently associated with alcohol in the genesis of hepatic cirrhosis. He regarded alcohol as an important factor, but one often associated with chronic infection in the production of cirrhosis.

Grenet, Levent, and Pellisier² stated that they had never seen a proven case of Laennec's cirrhosis due to syphilis without alcoholism. They believed it probable that excessive use of alcohol (which could produce cirrhosis by itself) lowered the resistance to syphilis, and that syphilis increased the progress of fibrosis.

The long established association of alcoholism with Laennec's cirrhosis and the work of Opie on the production of cirrhosis by combined infection and intoxication suggested the desirability of determining the frequency of alcoholism, occurring alone or in combination with syphilis, in the cases studied. In the 45 cases of diffuse cirrhosis there were 12 in which the history contained no mention of the alcoholic habits of the patient. These were classified as "unknown." In the rest, consumption of alcohol was classified arbitrarily as "excessive," "moderate," and "none." Only those with a history of excessive use of alcohol were regarded as significant though the others were tabulated (Table 3).

TABLE 3.—INCIDENCE OF ALCOHOL IN CASES OF CIRRHOSIS.

Type of cirrhosis.	No.	Consumption of alcohol.				Combined alcoholism and syphilis.
		Excessive.	Moderate.	None.	Unknown.	
Diffuse	45	16	8	9	12	5
Syphilitic	2			1	1	
Obstructive	8	1	2	2	3	
With tumor	7	1	1	3	2	
Central	2				2	
Miscellaneous	10	1		6	3	1
Total	74	19	11	21	23	6

Syphilis was thus (Table 2) associated with diffuse cirrhosis of the liver in 13 out of 45 cases (28.8%). Alcoholic excess was present in 16 (35.5%) of the cases. The two factors were coëxistent in 5 (11.1%) of the cases. If the cases in which alcoholic habits were unknown were excluded, the proportion of cases in which alcoholic excess occurred alone was 48.5%, and the proportion in which both factors were present, 15.1%.

The sex distribution of all the cases of diffuse cirrhosis was compared with that of the cases of diffuse cirrhosis associated with syphilis. In the entire group of cases of diffuse cirrhosis there was a preponderance of males (78%) over females (22%). This preponderance was even more striking in the group with syphilis, all cases of cirrhosis with syphilis being in males.

The average age of all cases of diffuse cirrhosis (51.2 years) was approximately the same as that of the group with syphilis (53 years). In both groups approximately two-thirds of the cases were in the fifth or sixth decade of life.

An effort was made to determine whether there was any correlation between cirrhosis and the duration of the luetic infection. In 7 of 13 cases the approximate duration of infection was known, and had been from 10 to 25 years in 6; in a seventh case the duration of the disease was said to have been "some years." Information regarding treatment was at hand in only 6 cases and, of these, 5 had had treatment of varied duration and 1 had none.

It is noteworthy that in 45 cases of diffuse cirrhosis there was one instance of Graves' disease and one of nodular toxic goiter.

To compare the incidence of syphilis unaccompanied by cirrhosis with that in individuals with cirrhosis, 45 autopsies on patients of the same age and sex as the 45 with diffuse cirrhosis were chosen otherwise at random from the postmortem files. The presence of syphilis in these was determined in the same manner as before, namely by study of the history, clinical findings, laboratory findings, and autopsy protocols. The history with regard to the use of alcohol was noted in each case. Of 45 cases there were only 2 (4.4%) with syphilis, and both of these, with 4+ Wassermanns during life, had syphilitic aortitis at autopsy. Only half of the histories mentioned the presence or absence of excessive intake of alcohol, of which two definite instances were found. The following table summarizes the data obtained from the control group:

TABLE 4.—INCIDENCE OF SYPHILIS, ALCOHOLISM, AND COMBINED FACTORS IN A CONTROL GROUP OF 45 CASES WITHOUT CIRRHOSIS.

	No.	Per cent.
Syphilis	2	4.4
Alcohol in excess	2	4.4
Alcohol in moderation	8	
No alcohol	13	
Alcoholic habits unknown	22	
Syphilis and alcoholic excess	0	0.0

Postmortem records of all the definitely proven cases of syphilis which came to autopsy in the new New York Hospital during 4 years were reviewed to determine the incidence of cirrhosis. Study of the records and microscopic sections revealed among them 3 cases of diffuse cirrhosis, 1 classified as scant or beginning cirrhosis, the other 2 as moderately advanced. Of the latter, 1 had a history of excessive use of alcohol. There were in addition 5 cases of cirrhosis of other types. These data are shown in Table 5.

TABLE 5.—INCIDENCE OF CIRRHOSIS IN 24 CASES OF CLINICALLY PROVEN SYPHILIS THAT CAME TO AUTOPSY.

Cases of syphilis		24
Diffuse cirrhosis		3
Other types:		
Obstructive cirrhosis	2	5
Cirrhosis with carcinoma	2	
Syphilitic (hepar lobatum)	1	
No cirrhosis		16

The foregoing tables show that syphilis and alcoholism and the two combined are much more frequent in association with diffuse cirrhosis of the liver than in persons of the same age and sex with no cirrhosis of the liver. Of 45 persons with diffuse cirrhosis of the liver, at least one-fourth and probably more have had syphilis. Of a small group of persons with syphilis several (3 of 24) had developed cirrhosis.

Summary. 1. Of 45 cases of diffuse cirrhosis including 44 cases of nodular or Laennec's cirrhosis and 1 case of smooth hypertrophic cirrhosis of the type of Hanot, 28.8% had presumptive evidence of syphilis; approximately one-third were known to have used alcohol in excess, or approximately one-half if those cases were excluded whose alcohol habits were unknown; and 11.1% were both luetic and alcoholic (15.1% when the unknowns were excluded).

2. Approximately three-quarters of the cases of diffuse cirrhosis and all of those with diffuse cirrhosis and syphilis were in men. Among the cases in which the duration of infection was known, that is, in less than half of them, there was no instance in which syphilis had been present for less than 10 years.

3. A control group of 45 autopsies with no cirrhosis in persons of the same age and sex as those with diffuse cirrhosis showed that 2 (4.4%) had had syphilis, and 2 had used alcohol in excess. The two factors were combined in no instance.

4. In a group of 24 autopsies on persons with syphilis, diffuse cirrhosis of the liver was found in 3 cases (12.5%).

5. Syphilis long continued in association with alcoholism, and perhaps alone, may cause diffuse cirrhosis of the liver.

REFERENCES.

- (1.) Cade, A.: *Rev. med. Chir. d. Mal. du Foie*, 2, 500, 1927. (2.) Grenet, H., Levent, R., and Pellisier, H.: *Ibid.*, p. 311. (3.) Hawkins, H. P.: *Albutt and Rolles-*

ton's System of Medicine, 4, 173, 1906-11, New York, The Macmillan Company. (4.) Hektoen, L.: J. Path. and Bact., 7, 214, 1901. (5.) LeDuc, D. M.: Ann. Int. Med., 2, 932, 1929. (6.) Ogata, S.: J. Med. Res., 40, 103, 1919. (7.) Opie, E. L.: J. Exp. Med., 12, 367, 1910. (8.) Owen, L. J.: Am. J. Syph., 5, 20, 1921. (9.) Pearce, R. M.: Arch. Int. Med., 6, 478, 1910. (10.) Rolleston, H. D., and McNee, J. W.: Diseases of the Liver, Gall-bladder, and Bile Ducts, New York, The Macmillan Company, 1929. (11.) Symmers, D.: Internat. Clinics, Ser. 27, 1, 58, 1917. (12.) Villaret, M., and Blum, P.: Rev. Med. Chir. d. Mal. du Foie, 1, 401, 1926. (13.) Villaret, M., Benard, H., and Blum, P.: Médecine, 3, 766, 1922; Arch. des Mal. de L'App. Dig., 12, 305, 1922. (14.) Whipple, G. H., and Sperry, H. J.: Bull. Johns Hopkins Hosp., 20, 278, 1909. (15.) Wooley, P. G.: Am. J. Syphilis, 1, 649, 1917.

LEIOMYOMA OF THE SMALL INTESTINE.

WITH REPORT OF A CASE WITH FATAL HEMORRHAGE.

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INTESTINAL obstruction through intussusception is generally emphasized as the commonest surgical complication of small intestinal tumors. In primary leiomyomas, however, a review of the literature indicates that grave hemorrhage is equally frequent, and likewise is amenable to surgical intervention if the patient is fortunate enough to be subjected to laparotomy. In such myomas, focal areas of hemorrhagic necrosis are common, and with their confluence the liquefied center may discharge into the lumen of the intestine, this being followed by copious hemorrhage. Exsanguination with syncope and even death is not uncommon under these circumstances. If the bleeding does subside, it almost invariably recurs. Only through surgery can this group of patients be saved. Too frequently, as in the case to be reported, the exact diagnosis is discovered at the autopsy table following fatal exsanguination.

Case Report. A 58-year-old white farmer, previously in good health, vomited copiously at noon on the day following a 300-mile motor trip, and that evening, after severe upper abdominal pain had appeared, profuse emesis recurred. Blood was not visible in the vomitus, and a large fluid stool was not inspected. Upon admission 2 days later to hospital, October 24, 1935 (service of Dr. T. Grier Miller), he was very restless despite sedation, his hemoglobin being 49% and his red cell count 2,900,000. The stools consisted of dark semifluid blood. No mass could be palpated through a well-relaxed abdominal wall. A surgical consultant concurred in the tentative diagnosis of duodenal or jejunal ulcer, and a medical regimen was outlined. He received large transfusions of blood daily, but succumbed from the persistent hemorrhage on the 7th day of his illness.

Autopsy (No. 35-1306, Dr. H. M. Dixon, 1 hr. after death) disclosed less senescent change than was to be expected, but marked ischemia of all organs. The lower half of the ileum and the colon were filled with approximately 2 liters of reddish-black semifluid blood. On the antimesenteric border of the ileum, 220 cm. above the ileocecal valve, its coarsely nodular surface

covered with intact peritoneum, was a 4 cm. spheroidal tumor that had undergone massive central liquefaction and evacuation through a narrow channel into the intestinal lumen. The cavity was pear-shaped, filled with partially clotted blood, and on first inspection was thought to be a Meckel's diverticulum with an annular neoplasm encircling its orifice. Its wall was lined by a smooth layer of necrotic debris, exhibiting the patent lumen of an eroded arteriole. The intestinal tract above this point was grossly normal and virtually empty. No metastases were found.

Microscopic Examination. The tumor showed whorls of smooth muscle cells interspersed with scant connective tissue (confirmed with Van Gieson's stain). The muscle cells exhibited the following cytological characteristics commonly considered as evidence of malignancy from the histopathologic standpoint: short cells with ovoid nuclei, marked variation in size and shape of the tumor cells, variable staining affinity of the nuclei, "giant cells" with multiple nuclei, and extremely thin-walled blood-vessels. No typical mitotic figures were demonstrable. Both layers of the intestinal muscle were interrupted by the tumor, leaving little evidence as to which one was primarily the seat of the neoplasm. The lining of the cavity wall consisted of necrotic debris and inflammatory exudate harboring bacterial colonies, but entirely devoid of mucous membrane. The distal wall of the cavity also consisted of tumor tissue rather than the components of a Meckel's diverticulum, while the peritoneal serosa was intact and free of exudate or adhesions. The tissue has been examined and the diagnosis of "malignant leiomyoma" substantiated by Dr. Joseph McFarland and Dr. Krumbhaar.

The *incidence* of leiomyoma in the alimentary tract is reflected in Table 1. Raiford⁶ found 3 myomas among the 82 primary tumors of the small intestine in the Johns Hopkins Hospital records, while Rankin and Newell⁷ reported 11 myomas among 35 benign small intestinal tumors from the Mayo Clinic. This leaves little doubt that myomas of the small intestine are far more frequent than the number of reported cases (109) would suggest.

TABLE 1.—CASES OF LEIOMYOMA OF THE ALIMENTARY TRACT.

Site.	Recent reviews in the literature.	Among 36,000 autopsies at Philadelphia General and University Hospitals (not previously reported).
Esophagus	50 ⁸ (all at autopsy)	2
Stomach	321 ³	18
Small intestine	109 (this report)	8
Large intestine	33* ¹⁰	5

* With 51 cases in small intestine.

In a *classification* by Steiner¹¹ of small intestinal leiomyomas according to their relation to the lumen of the intestine, those projecting into the lumen and predominantly submucosal were called "inner" myomas, while those extending into the peritoneal cavity were described as "outer." No asymptomatic inner myomas have been reported; when located in the duodenum, partial obstruction or ulcer-like pain is common; when situated below the ligament of Treitz, intussusception is the usual result. They remain small and rarely exceed 4 cm. in diameter. The outer myomas grow much larger, often being compared in size to an infant's head, and undergo

focal hemorrhagic necrosis; these areas tend to merge and rupture by permeation through the tumor tissue into the intestinal lumen. The pear-shaped conformation of the resultant cavity closely resembles the pregnant uterus, and the mechanism of the subsequent hemorrhage is somewhat comparable to that of postpartum inertia uteri. Such a shell of tumor tissue grossly mimics a diverticulum, and despite the absence of mucosal lining, at least one specimen¹² strikingly similar to the one here reported has been recorded as a primary leiomyoma of a Meckel's diverticulum.

The *rate of growth* in these tumors appears to be remarkably slow, often stationary. In a number of patients, symptoms persisting for several decades have been alleviated by extirpation of a myoma measuring but a few millimeters in diameter.

The *degree of malignancy* of a leiomyoma cannot be accurately determined upon histologic criteria. Doring² and McFarland⁵ have pointed out that the only positive proof of malignancy in this tumor is the presence of metastases. As in our own case, many authors have classified their specimens as malignant upon cytologic grounds, but from the clinicians' standpoint, it is noteworthy that only 9 of the 109 tumors reviewed did metastasize. Recurrences have made their appearance years after removal of the original lesion.

Previous reports present meager clinical data for proper analysis. Most of the specimens were reported purely because of their pathologic interest; some were not adequately confirmed histologically; some were presented soon after surgical extirpation without pertinent clinical details; and finally, the nomenclature of this tumor has often changed during the 80 years since the first acceptable report.

I have rejected the reports of certain specimens which consisted preponderantly of fibrous tissue with admixture of muscle cells. I have taken certain license in assuming the location or outcome in some instances when the report implied but did not specifically state such details. The following remarks are intended to supplement the data presented in Chart I.

Inner leiomyomas have not been reported as incidental autopsy discoveries in the absence of antecedent symptoms, but the assumption that few remain asymptomatic is probably fallacious. Whether sessile or pedunculated, they are most frequently likened in size to various nuts or eggs. They are three times as common in the jejunum and ileum as in the duodenum, which accounts for the preponderance of intussusception. No metastases or recurrences have been reported in this group, and only 3 deaths have been cited in the past 25 years.

Ordinary gastro-intestinal Roentgen study may display a defect due to a duodenal myoma, but below the ligament of Treitz it has not been useful in the diagnosis of these tumors. At this hospital, Abbott¹ has conclusively demonstrated a tumor of the jejunum by intestinal intubation, introducing the barium mixture proximal to an

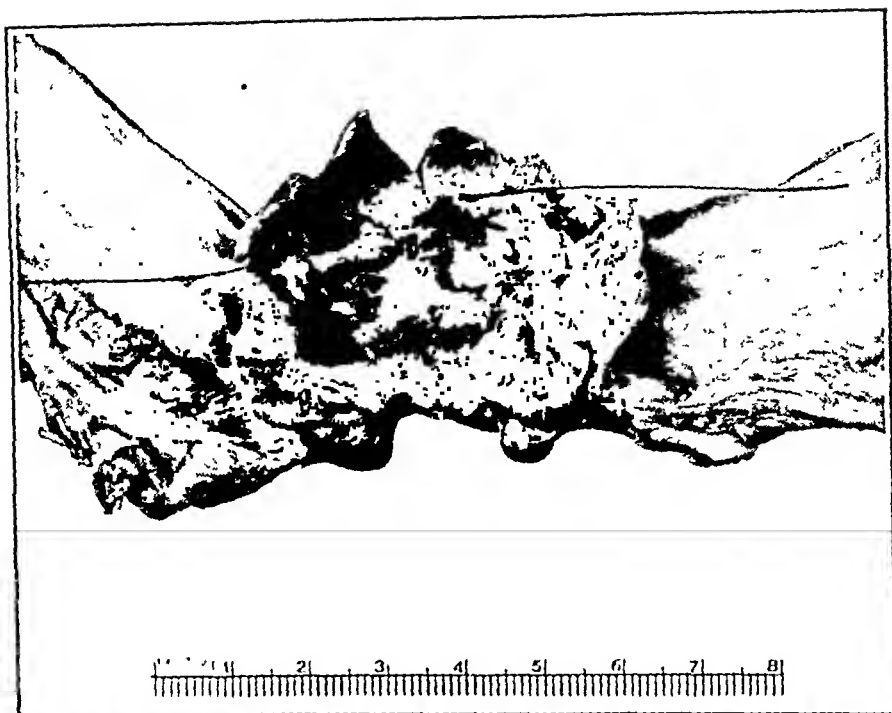
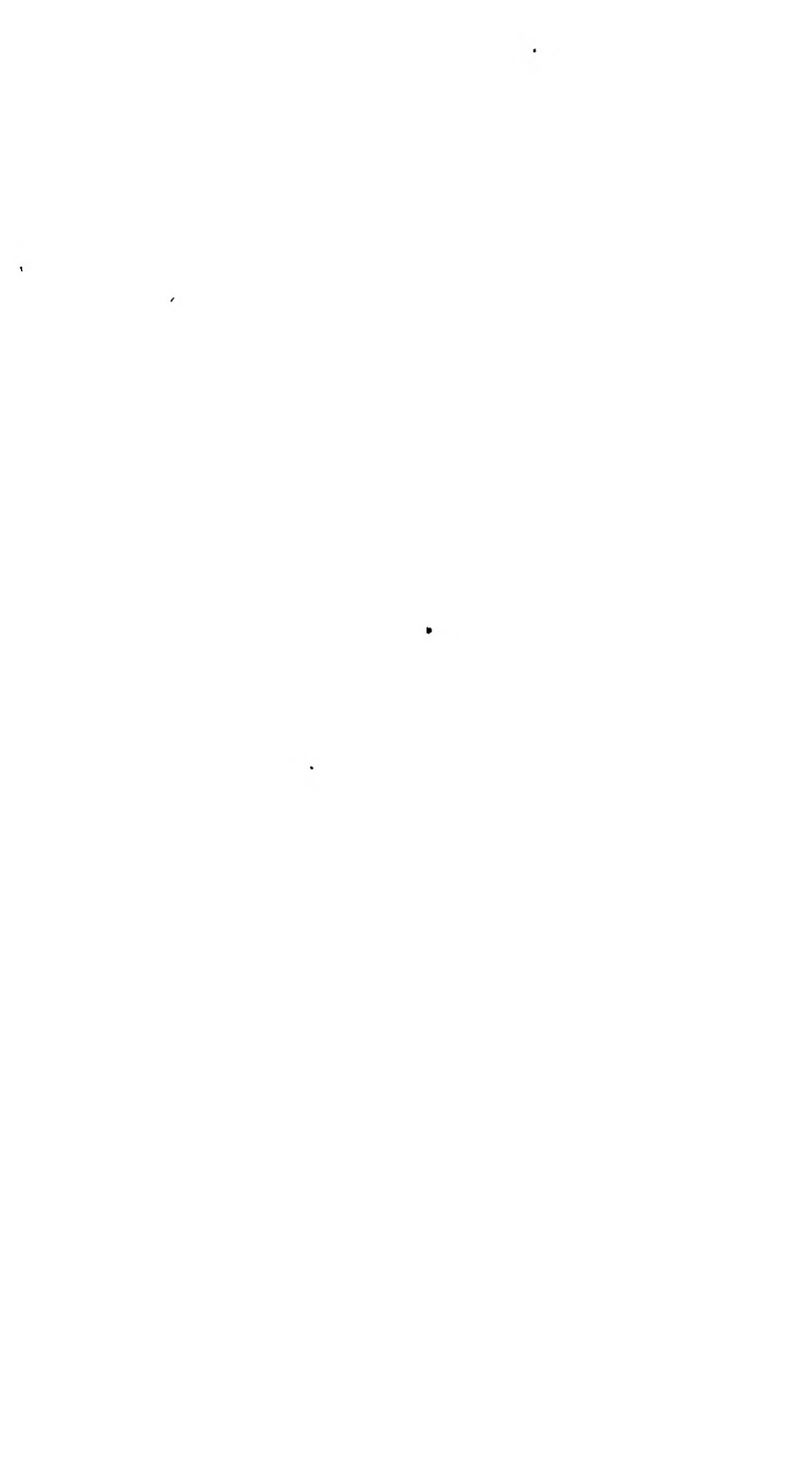


FIG. 1.—Photograph of the opened tumor and serosal surface of the intestine; note the coarsely nodular wall, and the hair inserted in the eroded arteriole. Most of the tumor tissue forms an annular mass around the orifice of the pseudodiverticulum.



FIG. 2.—Photomicrograph of tumor tissue (hematoxylin-eosin, $\times 280$)



Acute intestinal obstruction¹³ from intussusception or invagination occurred in 62% of the myomas located in the free-lying jejunum and ileum, but this does not occur in the duodenum which is retroperitoneal and fixed. The average age of these patients is conspicuously low in comparison with the other groups. Most of the tumors were less than 4 cm. in diameter, while the largest measured 12 cm. The only death in this group since 1910 occurred from bronchopneumonia a fortnight after resection. Recurrent acute or persistent partial obstruction¹⁴ occurred in 7 patients over periods of months or years. Their average age is high.

All but one of the 7 cases of hemorrhage¹⁵ experienced rather sudden weakness followed by the passage of copious tarry stools. Similar attacks recurred in 4 cases, and 6 were eventually cured by surgery. The seventh patient was hospitalized in a moribund condition from the exsanguination and soon succumbed. The tumor in these cases was usually less than 2 cm. in diameter and superficially ulcerated.

Newell and Rankin have emphasized the ulcer-like pain¹⁶ which is produced by small submucosal myomas in the duodenum or jejunum. Only 1 of their 4 tumors exceeded 4 mm. in diameter.

The single instance of icterus¹⁷ was cured by removal of a walnut-sized polypoid myoma lying just above the ampulla of Vater.

Outer leiomyomas are almost twice as frequent as the inner type. They tend to become much larger with increasingly conspicuous hemorrhagic cystic necrosis, and are often compared in size to a child's head. Spontaneous hemorrhage is the most common symptom and tends to persist or recur. Roentgenologic assistance in the diagnosis is not to be anticipated by conventional methods, since the barium meal is not impeded and the intestinal lumen is not distorted in any characteristic fashion.

The mechanism of hemorrhage²² from outer leiomyomas is schematically presented in Chart II. Bleeding is rather rare in myomas of the duodenum, but appears in a preponderant number of those located in the jejunum and ileum. Only 6 of the 22 patients in this group were saved by surgical intervention. Five died of hemorrhage, 3 of pulmonary embolism (1 postoperative), and 2 of postoperative peritonitis.

Approximately 20% of the outer myomas were unexpectedly discovered at autopsy or laparotomy (asymptomatic²⁰), in decided contrast to the inner leiomyomas. The 3 encountered at laparotomy for other reasons were successfully resected.

Thirteen patients had noted an abdominal mass¹⁸ before they sought medical attention, although chronic digestive symptoms had been disregarded by most of them. Several of the tumors were "the size of a man's head," and central hemorrhagic necrosis was commonly mentioned in the descriptions.

Torsion or volvulus accounted for the cases of acute intestinal

obstruction,¹⁹ while less clear-cut mechanical distortion presumably explains the more prolonged obstructive symptoms.²¹

The few cases tabulated under "indigestion"²³ include only those not properly classified elsewhere, and does not sufficiently emphasize the digestive symptoms which are commonly cited, *e. g.*, alter-

THE GENESIS OF FATAL HEMORRHAGE FROM SUBSEROSAL "OUTER" LEIOMYOMATA



ASYMPTOMATIC

FIRM, NODULAR, GREY-RED CUT SURFACE, SLOW-GROWING, EGG-SHAPED, USUALLY ANTIMESENTERIC & PERPENDICULAR TO THE INTESTINE AXIS
MINOR SUBMUCOSAL ELEVATION WITHOUT ULCERATION
VERY RARE METASTASES DESPITE MALIGNANT CYTOLOGY.
NO X-RAY DEFORMITY UNLESS TUMOR IS RETROPERITONEAL (DUODENAL).



INTERSTITIAL HEMORRHAGES

COMMONLY PRESENT EXCEPT IN SMALLEST SIZED MYOMATA



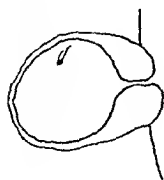
CONFLUENCE OF HEMORRHAGIC NECROTIC AREAS

MASSIVE CENTRAL LIQUIFACTION NECROSIS LARGELY DUE TO PRESSURE ISCHEMIA SECONDARY TO HEMORRHAGE
EROSION OF ARTERIES & VEINS



EVACUATION INTO THE INTESTINE

PERMEATION THROUGH MYOMA ALONG LINES OF CLEAVAGE BETWEEN WHORLS OF CELLS FORMING A NARROW FISTULA EMERGING AS A SMALL SLIT OR FISSURE PEAR-SHAPED CAVITY
INTRAPERITONEAL EVACUATION OCCURS ONLY AFTER TRAUMA



PERSISTENT BLEEDING

FIRM CAVITY WALLS & FREE DRAINAGE HINDER CESSATION OF ARTERIAL HEMORRHAGE BY NORMAL CLOTTING MECHANISM
STOOL: DARK RED-BLACK LIQUID & CLOTTED BLOOD.

DEATH OR SURGICAL CURE

CHART II

nating diarrhea and constipation, abdominal discomfort or pain, a feeling of distention, gaseous eructation, and loss of appetite. In this group is included the first surgical cure of this condition (Babes and Nann, 1897).

In 3 instances where the tumor reached quite large proportions,

rupture²⁴ of the necrotic areas into the peritoneal cavity occurred. One physician had the misfortune to have this occur during palpation of the cystic mass. This tumor was extirpated, recurred 5 years later, and was again successfully removed.

Summary. Myomas of the small intestine in general produce symptoms during middle age or later. Inner myomas tend to produce intestinal obstruction by intussusception, hemorrhage by superficial ulceration, or ulcer-like pain perhaps through traction stimulation of the mucosa. Outer myomas are particularly prone to dangerous hemorrhage, are frequently found unexpectedly at laparotomy or autopsy, may reach such size as to attract the patient's attention, and may by mechanical stress produce intestinal obstruction, more commonly partial than complete. As a rule, conventional Roentgen studies have not given material assistance in the diagnosis of this tumor, but the method of intestinal intubation together with radiologic examination (Abbott¹) may prove helpful.

An instance of probably preventable death due to persistent hemorrhage from a small outer myoma of the ileum is reported, stressing the justification of exploratory laparotomy in patients whose persistent enterorrhagia does not seem explicable upon the basis of bleeding ulcer.

A schematic analysis of the symptomatology of this tumor is presented, based upon 109 recorded cases.

Conclusions. 1. Inner (submucosal) leiomyomas of the small intestine tend to remain small and commonly produce symptoms which lead to surgical intervention and a high percentage of cures. No metastases have been reported.

2. Outer (subserosal) leiomyomas grow much larger, frequently attracting the patient's attention through their size. Metastases or recurrence occurred in 16% of this group. Progressive central liquefaction necrosis in the tumor, with evacuation into the intestinal tract, produces a pseudodiverticulum from which, unless operation is performed, severe enterorrhagia is apt to continue until death.

REFERENCES.

- (1.) Abbott, W. O.: Personal communication.
- (2.) Doring, H.: *Monatsschr. f. Geburtsh. u. Gynäk.*, 83, 317, 1929.
- (3.) Eliason, E. L., Pendergrass, E. P., and Wright, V. W. M.: *Am. J. Roent. and Radium Ther.*, 15, 295, 1926.
- (4.) King, E. L.: *Surg., Gynec. and Obst.*, 25, 54, 1917.
- (5.) McFarland, J.: *Am. J. Cancer*, 25, 530, 1935.
- (6.) Raiford, T. S.: *Radiology*, 16, 253, 1931.
- (7.) Rankin, F. W., and Newell, C. E.: *Surg., Gynec. and Obst.*, 57, 501, 1933.
- (8.) Rose, J. D.: *Brit. J. Surg.*, 24, 297, 1936.
- (9.) Rydygier: *Deutsch. Ztschr. f. Chir.*, 42, 101, 1895.
- (10.) Staemmler, M.: *Neue Deutsche Chirurgie*, Bd. 33a, Ferdinand Enke, Stuttgart, 1924.
- (11.) Steiner, R.: *Beitr. z. klin. Chir.*, 22, 407, 1898.
- (12.) Symmers, D.: *Ann. Surg.*, 70, 183, 1919.

(13.) INNER MYOMA: ACUTE INTESTINAL OBSTRUCTION. Albert: *Wien. klin. Wehnschr.*, 8, 476, 1895; Balog: *Zentralbl. f. Chir.*, 62, 802, 1935. Barthel: *Ibid.*, 5, 79, 1878. Boitche: *Arch. f. Heilk. von Wagner*, 11, 125, 1870. Bramann: Quoted by Rydygier⁹. Delore: *Lyon med.*, No. 20, p. 50, 1899 (Case 188). Delore and Leriche: *Rev. de Chir.*, 38, 39, 1908. Dixon and Steward: *Surg., Gynec. and Obst.*, 56, 801, 1933. Elliott and Corscaden: *Ann. Surg.*, 53, 169, 1911. Fleiner:

Virch. Arch., 101, 484, 1885. Haasler: Arch. f. klin. Chir., 68, 817, 1902. Hopfer: Ibid., 97, 1058, 1912. Lockwood: Brit. Med. J., 1, 966, 1892. Nonne: Deutsch. med. Wehnschr., 48, 144v, 1894 (also Geissler, Inaug. Diss., Marburg, 1894). Pantzer: Am. J. Obst., 68, 955, 1913. Plenk: Wien. klin. Wehnschr., 40, 556, 1927. Salzer: Ann. Surg., 45, 730, 1907. Schlätzler: Quoted by Steiner.¹¹

(14.) INNER MYOMA: CHRONIC INTESTINAL OBSTRUCTION. Bertel: Boll. de Soc. med.-chir. di Modena, 34, 310, 1934. Carle: Quoted by King.⁴ Fenger: Chicago Clin. Rev., 4, 107, 1894. Glass and Alsberg: Deutsch. med. Wehnschr., 48, 1108, 1922. Hauswirth: Beitr. z. klin. Chir., 89, 209, 1914. Rankin and Newell: Surg., Gynec. and Obst., 57, 501, 1933 (2 cases). Schildt: Acta Chir. Scand., 63, 77, 1928. Selby: Brit. Med. J., 2, 1578, 1897.

(15.) INNER MYOMA: CHRONIC ULCER SYMPTOMS. Rankin and Newell: Surg., Gynec. and Obst., 57, 501, 1933 (4 cases).

(16.) INNER MYOMA: HEMORRHAGE. Cabot: New England Med. J., 202., 685, 1930. Camp: Radiology, 2, 262, 1924. Hake: Beitr. z. klin. Chir., 78, 414, 1912. Linsmayer: Arch. f. klin. Chir., 114, 235, 1920. Rankin and Newell: Surg., Gynec. and Obst., 57, 501, 1933. Schildt: Acta Chir. Scand., 63, 77, 1928 (2 cases).

(17.) INNER MYOMA: ICTERUS. Wendel: München. med. Wehnschr., 72, 285, 1925.

(18.) OUTER MYOMA: ABDOMINAL MASS. Bagozzi: Tumori, 8, 110, 1934. Bonneau: Bull. et mém. Soc. de Chir. de Paris, 20, 52, 1928. Demel: Virch. Arch., 261, 881, 1926; 269, 160, 1928. Dixon and Steward: Surg., Gynec. and Obst., 56, 801, 1933. Hedlund and Hellström: Zentralbl. f. Chir., 29, 28, 1902. Key-Aberg: Acta Chir. Scand., 62, 261, 1927. Knorre: Deutsch. Ztschr. f. Chir., 246, 124, 1935. Lieblein: Beitr. z. klin. Chir., 41, 571, 1904. Prokopyeff: Quoted by King.⁴ von Salis: Deutsch. Ztschr. f. Chir., 160, 180, 1920. Steindl: Wien. med. Wehnschr., 79, 1256, 1929 (2 cases). Wolfram: St. Petersburger med. Wehnschr., N.F., 19, 2, 1902.

(19.) OUTER MYOMA: ACUTE INTESTINAL OBSTRUCTION. Benoit and Alivisatos: Bull. et mém. Soc. nat. de Chir., 60, 1221, 1934. Boerma: Zentralbl. f. Gynec., 53, 1717, 1929. Brocq and Hertz: Rev. de Chir., 59, 377, 1921. Caro: Berlin klin. Wehnschr., 32, 726, 1896. Moir and Walker: Brit. Med. J., 2, 1170, 1928. Pontoppidan: Quoted by Key-Aberg.¹⁸ Valan: Quoted by Staemmler.¹⁰ Wesener: Virch. Arch., 93, 377, 1883.

(20.) OUTER MYOMA: ASYMPTOMATIC. Christeller: Zentralbl. f. allg. Path. u. path. Anat., 33, 175, 1922-23. Förster: Virch. Arch., 13, 270, 1858. Fried: Inaug. Diss., Erlangen, 1902. Frötscher: Deutsch. med. Wehnschr., 35, 1263, 1909. Hansemann: Virch. Arch., 144, 400, 1896. Hirschel: Ibid., 177, 167, 1904. Kathe: Ibid., 187, 265, 1907. Petrow: Quoted by Steiner.¹¹ Priesel: Quoted by Demel.¹⁸ Puskeppelies: Virch. Arch., 240, 361, 1923. Rankin and Newell: Surg., Gynec. and Obst., 57, 501, 1933. Rieckenberg: Inaug. Diss., München, 1911. Symmers: Ann. Surg., 70, 183, 1919. Wesener: Virch. Arch., 93, 377, 1883. Wood: Proc. New York Path. Soc., 1, 52, 1901.

(21.) OUTER MYOMA: CHRONIC INTESTINAL OBSTRUCTION. Fischer: Berlin klin. Wehnschr., 50, 235, 1913. Kukula: Wien. klin. Rundschau, 9, 305, 1895. Lode: Wien. klin. Wehnschr., 7, 381, 1894. Lorenz: Ibid., 27, 1401, 1905.

(22.) OUTER MYOMA: HEMORRHAGE. Anderson and Doob: Arch. Path., 16, 795, 1933. Author's case. Brink and Laing: Arch. Path., 15, 316, 1933. Demmin: Aerztl. Sachverst.-Ztg., 18, 76, 1912. Egtermeyer: Inaug. Diss., Greifswald, 1920. Finney: J. Am. Med. Assn., 100, 408, 1933. Ghon and Hintz: Beitr. z. path. Anat. u. z. Allg. Path., 45, 89, 1909. Goldschmidt: Deutsch. Ztschr. f. Chir., 178, 128, 1923. Haggard and Floyd: Am. J. Surg., 28, 428, 1935. Hässner: Frankf. Ztschr. f. Path., 14, 501, 1913. Klopp and Crawford: Ann. Surg., 101, 726, 1935 (2 cases). Lauche: Virch. Arch., 252, 39, 1924. Mercier: Med. Rec., 33, 67, 1888. Pugliatti: Clin. Ostet., 36, 702, 1934. Ranzi: Verhändl. d. Ges. Deutscher Naturf. u. Aerzte, 85, 403, 1913. Richter: Deutsch. Ztschr. f. Chir., 102, 237, 1909. Rohdenburg: J. Lab. and Clin. Med., 4, 434, 1919. Rosenow: Deutsch. med. Wehnschr., 38, 1785, 1912. Steindl: Wien. med. Wehnschr., 79, 1256, 1929. Steiner: Beitr. z. klin. Chir., 22, 1, 1898. Wortmann: Deutsch. Ztschr. f. Chir., 123, 103, 1913.

(23.) OUTER MYOMA: INDIGESTION. Babes and Nanu: Berlin klin. Wehnschr., 34, 138, 1897. Carle: Quoted by King.⁴ Hult: Deutsch. med. Wehnschr., 32, 944, 1906. Klopp and Crawford: Ann. Surg., 101, 726, 1935. Marwedel: Beitr. z. klin. Chir. (Suppl. 7), 24, 104, 1899.

(24.) OUTER MYOMA: RUPTURE AND PERITONITIS. Cattell and Woodbridge: Surg. Clin. North America, 11, 363, 1931. Matthews: Arch. Surg., 10, 720, 1925. Puskeppelies: Virch. Arch., 240, 361, 1923.

STUDIES OF MYOHEMOGLOBIN AT HIGH ALTITUDES.

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THE process of adaptation to a low barometric pressure has been a subject of interest to physiologists for a good century. In spite of numerous observations, however, we have not yet a precise knowledge of the basic mechanism which would explain the profound difference which exists between the newcomer and the native of the altitude. It seems to us that two main factors are responsible for the failure to disclose the fundamental aspect of the problem. First, is the constantly repeated attempt to interpret the changes which occur in men and animals during the first few days or weeks of residence at high altitude in terms of final adaptative processes; and, second, the relatively few investigations concerning the physiologic characteristics of men and animals who are born and raised in high places. It is unquestionable that only a thorough study of the latter will result in showing the mechanism or mechanisms, which are responsible for leading unrestricted physical and mental activities in a condition of constant anoxemia.

The important work of Whipple and his associates on muscle hemoglobin, to which we will make a detailed reference in the discussion of our findings, justifies assignment to this substance of an important rôle in muscle economy and work. The determination of this hemoglobin in animals (dogs) born and raised in high regions of the Peruvian Andes, and its possible significance from the point of view of adaptation to the altitude, has been the subject of the present investigation.

Material and Methods. For comparative purposes we selected 7 healthy adult dogs (Nos. 1 to 7) born and raised in Lima (sea level). These dogs were placed on a uniform diet (meat, potatoes and rice) for 8 weeks previous to the determination of muscle hemoglobin. A moderate degree of physical activity was allowed.

At high altitude we selected 7 other healthy adult dogs: 4 of these (Nos. 8 to 11) were born and raised in Morococha (at 14,890 feet with an average barometric pressure of 415 mm. Hg); and the last 3 (Nos. 12 to 14) were born and raised in Oroya (at 12,300 feet with an average barometric pressure of 485 mm. Hg). The dogs studied in Morococha were also placed on the same uniform diet for 8 weeks before the determination; those studied in Oroya were not subject to this previous observation.

The method followed was that of simultaneous bleeding and perfusion (Whipple⁹): the dog was placed under ether anesthesia, and by careful dis-

section of the neck one of the carotid arteries, and the external jugular vein on the opposite side, were exposed. Adequate cannulae were inserted in these vessels and warm, freshly prepared Locke's solution, from a graduated bottle was allowed to enter by gravity into the vein. Simultaneous bleeding was started from the artery and the blood received in a graduated cylinder. In every case the inflow and outflow were regulated so that the difference between the two would not exceed 50 to 100 cc., thus avoiding edema of the tissues. When the respirations and heart contractions began to show evident weakening and irregularities a subcutaneous injection of 0.5 cc. adrenal chloride was administered, in an effort to prolong the life of the dog as long as possible. The simultaneous perfusion and bleeding were carried on until the death of the dog; immediately after this the abdomen was opened and the vena cava cut. At the same time a moderate amount of Locke's solution was allowed to enter through the carotid artery and the perfusion continued for a short time, while the legs and trunk were massaged to expel the last traces of circulating blood. After this procedure the intestines, mesentery and lungs appeared macroscopically, in all cases, as being completely free of blood. In all determinations a hematocrit reading in the circulating arterial blood (using Wintrobe's hematocrit tube) was taken before the operation and just before death. In the dogs studied in Lima (sea level) the hematocrit figure *before* the operation averaged 47.4 % red cells; *afterwards* 1.1 % (variations between 0.5 and 1.6%). These figures indicate a thorough elimination of practically all the circulating blood.

At high altitude, perfusion and bleeding were considerably more difficult on account of the higher initial hematocrit (which averaged 59.2 % red cells in the 7 dogs) and consequently increased viscosity of the blood. Considerable more fluid was used in the perfusion, and in a few instances we failed to carry on the determination on account of clotting of the blood in the cannulae. In the 7 dogs which were finally studied the average hematocrit figure, after bleeding before death, was 2.4 % red cells; but in 4 this figure was less than 2% (Fig. 1). It must be mentioned that this figure cannot be considered as an ultimate indication of the thoroughness of the removal of circulating blood, because in all experiments the perfusion and bleeding were carried on for some time after death.

A red cell count and hemoglobin determinations were also made in the sample of blood taken before perfusion was started. For the hemoglobin determination a Hellige hemometer, previously calibrated, was used.

A careful dissection of the muscles was performed immediately after the above procedures. For this purpose four different groups were selected: the adductors of the legs; the pectorals of the chest; the diaphragm and finally the heart. All the fat and fascia were removed as carefully as possible; the muscle was finely divided and cut, and portions of 10 gm. were very carefully weighed, using a sensitive scale. In all cases duplicate samples were obtained. The hemoglobin of the muscles was then extracted using a 0.4% ammonium hydroxide solution, and this extraction carried out for 24 hours in the ice box. Then the extracts were filtered and changed to an acid hematin solution by the addition of concentrated HCl. For comparative purposes we used a similar solution of human blood, in which the hemoglobin content had been carefully determined, using the Van Slyke and McNeil⁶ manometric method. The final comparison was made in a Dubosecq colorimeter and the final figure represented the average of the figures obtained in the two samples.

Results. See Table 1 for changes in the peripheral blood. In the dogs observed at high altitude there is a considerable higher level of circulating red cells and hemoglobin, and also a greater proportion

of red cells to plasma. Thus we find an average increase of 1.85 millions red cells per c.mm. in this group of animals as compared with the ones studied at sea level, and there is also a correspondent increase of 6.3 gm. of Hb. per 100 cc. of blood and 11.8% red cells

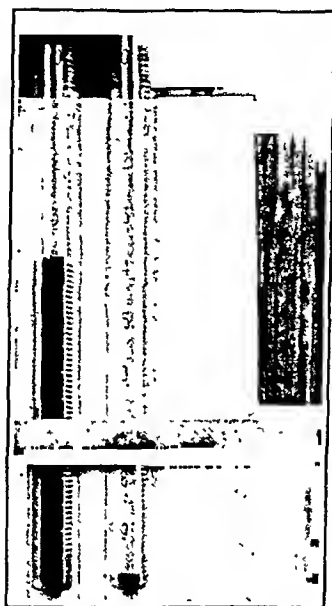


FIG. 1.—Dog 10, high altitude. Hematocrit determination (Wintrobe) in the circulating blood; 1, before simultaneous perfusion and bleeding was started and, 2, just before the death of the dog.

TABLE 1.—BLOOD VALUES IN THE OBSERVED DOGS.

(Determinations made in the circulating blood.)

SEA LEVEL.					ALTITUDE.				
Dog No.	Wt. (kilo).	Red cells (mill. per mm. ³).	Hemo-globin (gm. per 100 cc.).	Hematocrit % (red cells).	Dog No.	Wt. (kilo).	Red cells (mill. per mm. ³).	Hemo-globin (gm. per 100 cc.).	Hematocrit % (red cells).
1	6.20	8	14.4	7 90	19.4	57.9
2	6.50	8.04	17.2	58.8	9	10.0	6.84	18.2	53.3
3	11.0	10	9.0	8.50	23.2	66.9
4	12.0	6.04	14.5	45.0	11	7.4	7.84	20.4	62.3
5	14.0	5.64	12.4	40.2	12	18.5	9.46	23.4	67.6
6	10.0	6.00	14.6	51.6	13	9.5	6.57	18.4	45.7
7	15.2	4.79	12.6	41.5	14	10.2	8.55	21.4	61.0
Averages.					Averages.				
10.7	6.10	14.3	47.4		11.3	7.95	20.6	59.2	

(hematocrit). These findings in the circulating blood correspond to the well known polycythemia of altitude and its significance does not require further discussion in this paper.

The results obtained in the muscle hemoglobin determinations are summarized in Table 2, and in a graphic form in Fig. 2. Both at

sea level and at high altitude the diaphragm and leg muscles contain more hemoglobin than the chest and heart muscles, in the order given, and these results agree with the observations made by Whipple⁹ a few years ago. At high altitude there is a well marked and decided increase in the hemoglobin content of the muscles. This

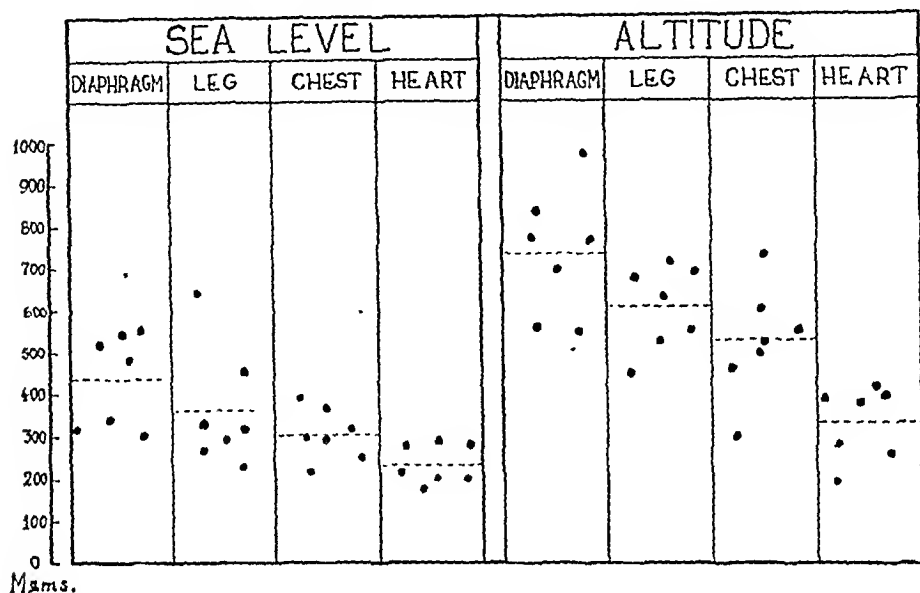


FIG. 2.—Determinations of myohemoglobin, expressed in mg. per 100 gm. of muscle, made in 7 dogs at sea level and in another 7 born and raised at high altitude. (Leg muscles: adductors; chest muscles: pectorals.) The dots correspond to the findings in each dog; the transverse lines represent the average value of all the determinations.

TABLE 2.—MILLIGRAMS OF MYOHEMOGLOBIN PER 100 GM. OF MUSCLE.

(Determinations made in 14 dogs.)

Dog No.	Wt. (kilo).	SEA LEVEL.				Dog No.	Wt. (kilo).	ALTITUDE.			
		Diaphragm.	Leg.	Chest.	Heart.			Diaphragm.	Leg.	Chest.	Heart.
		Mg. Hb. per 100 gm. muscle.						Mg. Hb. per 100 gm. muscle.			
1	6.2	321	294	296	206	8	14.4	696	532	499	285
2	6.5	483	320	322	220	9	10.0	560	451	463	256
3	11.0	520	453	394	296	10	9.0	549	557	302	194
4	12.0	340	273	224	204	11	7.4	764	688	551	415
5	14.0	301	232	252	174	12	18.5	837	712	604	377
6	10.0	552	643	372	277	13	9.5	966	679	723	399
7	15.2	547	337	299	285	14	10.2	771	632	525	395
Averages.											
10.7		438	365	308	237	11.3		735	607	524	331

is more accentuated in the diaphragm, leg and chest which exhibit an increase of 66 to 70% of this substance, as compared with the same group of muscles at sea level. The heart has about 40% more hemoglobin at high altitude. It is significant to find that in all the dogs studied in Oroya and Morococha the content of hemoglobin in each muscle is higher than the correspondent average figure found

at sea level. It is also interesting to notice that the diaphragm, which is a muscle subjected to an intense work at high altitude on account of the more frequent and deeper respirations, contains comparatively more hemoglobin than the other muscles: thus in Lima the diaphragm contains 73, 130 and 201 more mg. of Hb. per 100 gm. than the leg, chest and heart respectively, while at high altitude it contains 128, 211 and 404 more mg.

Comparing the increase of hemoglobin in the blood and in the striated muscle, we find that the latter is more marked: the hemoglobin shows a gain of about 44% in the blood of the dogs living under the influence of a low barometric pressure, while the striated muscles of these animals have 66 to 70% more of this substance as compared with those living at sea level.

Discussion. Although numerous observations have been made at high altitude on circulating hemoglobin, we are not aware of any previous work on the hemoglobin content of the muscles. Investigators have always been attracted to the problems of oxygen acquisition at lung level and its blood transport, disregarding what it appears to be the most important and fundamental aspect of adaptation: the adequate supply of oxygen, which is carried at a low tension, to the tissues.

The work of Whipple and his associates^{5,6,9,10} has shown that the hemoglobin contained in the muscles is a stable substance, not subject to wide variations even in conditions of anemia and deficient diet intake, in contrast with the labile character of the circulating hemoglobin. They have also demonstrated that the amount of myohemoglobin depends in large extent on the degree of muscular exercise and activity. This fact suggests at once that this substance plays an important rôle in muscle economy and work, being perhaps concerned with a rapid gaseous interchange. The observations carried out in dogs were confirmed in studies made in human autopsy material; Woodruff and Whipple¹¹ concluded that in man, as in the dog, the concentration of hemoglobin within the muscle fibers is determined more by the degree of muscular activity than by the level of blood hemoglobin.

The above findings give a special interest to the investigation of the amount of hemoglobin contained in the muscle fibers of animals fully adapted to a condition of chronic anoxemia in the altitude. Do they also show an increase of this substance and in this way the acquisition of O₂ by the tissues is greatly facilitated in spite of the low tension at which this gas is held in the circulating blood? Our findings seem to warrant an affirmative answer, and several considerations indicate that it is highly probable that the fundamental mechanism of adaptation lies at *tissue level*. Hurtado,⁴ in 1932, observed that although a large percentage of natives living in the Peruvian Andes exhibit supernormal circulating hemoglobin, there was a wide variation in this substance, and the degree of adaptation

had no relationship to its concentration. Guzmán Barrón, Dill, Edwards and Hurtado³ have recently demonstrated that the occurrence of Soroche (mountain sickness) does not have any relationship to the degree of anoxemia in the arterial blood, the O_2 and CO_2 tension in the alveolar air, or to the amount of hemoglobin in the blood; and they concluded that it is probable that the tissue system of transporting O_2 , of which the myohemoglobin is an important part, plays an important rôle in the mechanism of this syndrome. Dill, Edwards and Christensen² in the Chilean Andes failed to find any relationship between the degree of adaptation and the level of oxygen saturation in the arterial blood or the oxygen tension in the alveolar air.

The observations of Campbell¹ have special significance in this connection; this investigator found an elevated O_2 tension in the tissues of animals (rabbits) which showed a good adaptation to a low barometric pressure, in contrast with a low tension in those (cats, monkeys) which were poorly adapted to the abnormal environmental condition.

Clinically, there is a similarity between the symptoms found in Soroche and those of acute alcoholism, and Palthe⁷ demonstrated that the latter condition is essentially due to a state of tissue (histo-toxic) anoxemia.

The observations just mentioned emphasize the importance of considering adaptation in terms of mechanisms which operate at tissue level. Among these mechanisms it is likely that an increase of hemoglobin within the muscle fibers plays an important rôle and is perhaps one of the most fundamental adaptative processes in organism which are born and raised at high altitude, and which represents *adaptation* in its true significance.

Summary. Determinations of muscle hemoglobin by Whipple's method have been made in dogs born and raised at high altitude, and its results compared with similar observations made at sea level.

An increase of the hemoglobin content of the muscles has been found in the group of dogs at high altitude. It is suggested that this represents an important mechanism of adaptation to a condition of chronic anoxemia.

The senior author (A. H.) wishes to express his appreciation to Dr. G. H. Whipple for the kind personal demonstration of his method and the experience gained while working in his Department at the University of Rochester Medical School (1933).

REFERENCES.

- (1.) Campbell, J. A.: J. Physiol., 63, 325, 1927.
- (2.) Dill, D. B., Christensen, E. H., and Edwards, H. T.: Am. J. Physiol., 115, 530, 1936.
- (3.) Guzmán Barrón, E. S., Dill, D. B., Edwards, H. T., and Hurtado, A.: J. Clin. Invest., 16, 541, 1937.
- (4.) Hurtado, A.: Am. J. Physiol., 100, 487, 1932.
- (5.) Kennedy, R. P., and Whipple, G. H.: Ibid., 76, 685, 1926.
- (6.) Kennedy, R. P., and Whipple, G. H.: Ibid., 87, 192, 1928.
- (7.) Palthe, P. M. van W.: Deutsch. Ztschr. f. Herven., 92, 79, 1926.
- (8.) Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, vol. 2, Methods, Baltimore, The Williams & Wilkins Company, 1932.
- (9.) Whipple, G. H.: Am. J. Physiol., 76, 693, 1926.
- (10.) Whipple, G. H., Groth, A. H., and Robschit-Robbins, F. S.: Am. J. Physiol., 87, 185, 1928.
- (11.) Woodruff, W. W., and Whipple, G. H.: Am. J. Path., 4, 75, 1928.

BOOK REVIEWS AND NOTICES.

THE TREATMENT OF DIABETES MELLITUS. By ELLIOTT P. JOSLIN, M.D. (HARVARD), M.A. (YALE), Medical Director, George F. Baker Clinic, New England Deaconess Hospital; Clinical Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital. With the Coöperation of HOWARD F. ROOT, M.D., Physician, New England Deaconess Hospital; Instructor in Medicine, Harvard Medical School, PRISCILLA WHITE, M.D., Physician, New England Deaconess Hospital; Instructor in Pediatrics, Tufts College Medical School, and ALEXANDER MARBLE, M.D., Physician, New England Deaconess Hospital; Assistant in Medicine, Harvard Medical School. Pp. 707; 22 illustrations and 142 tables. Sixth Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, \$7.00.

MADE necessary by the discovery of protamine insulin, the new sixth edition gives information on this valuable new method of treatment that is based on experience in over 1200 cases. The author's experience extending over 39 years and with over 15,000 cases, and his consummate skill in presenting his material in an impressive and interesting way, continue to make this book not only the standard work on Diabetes but also one of the outstanding medical texts in the English language. R. K.

THE NORMAL ENCEPHALOGRAM. By LEO M. DAVIDOFF, M.D., Assistant Professor of Neurology in the College of Physicians and Surgeons, Columbia University; Attending Neurological Surgeon to the Neurological Institute of New York, New York City, and CORNELIUS G. DYKE, M.D., Assistant Professor of Radiology in the College of Physicians and Surgeons, Columbia University; Assistant Director in the Department of Radiology of the Neurological Institute of New York, New York City. Pp. 224; 149 illustrations. Philadelphia: Lea & Febiger, 1937. Price, \$5.50.

THIS monograph gathers together very well our knowledge of encephalography and encephalograms. The discussion of the technique of performing an encephalogram, the reactions that may follow the procedure and the means of counteracting them are fully detailed. The indications for and against the introduction of air by the lumbar route are considered. The shadows seen on the Roentgen ray film from air in the ventricles, the basilar cisternæ and the finer ramifications of the subarachnoid spaces are described and carefully correlated by good anatomical illustrations. Particularly important is the identification of air shadows seen in the basilar cisternæ and the cortical sulci.

The Reviewer can find but one fault with this excellent monograph. A part of an encephalogram is illustrated and the details are described as normal. This is done thoroughly and no area is omitted. But there is no whole encephalographic outline, antero-posterior, postero-anterior, and right and left lateral which is given as a normal. Nothing is said of normal variations from an accepted standard, for no accepted standard of normality throughout the whole ventricular, cisternal and subarachnoid space is set up. Although this monograph is based upon a study of 4000 cases, presumably all of them had some intracranial abnormality, otherwise an encephalo-

gram would not have been done. While, therefore, normal details of all brain areas could be found in this series, a group of encephalograms normal in every way could not be presented. But it is exactly this that the medical profession needs. Encephalograms are being introduced as evidence in medico-legal cases. Physicians are being called upon to state whether certain encephalographic changes can be relied upon to indicate brain injury which might produce definite symptoms.

This monograph is important for it sets up normals in encephalographic shadow detail in local areas, whereby abnormalities presumably pathologic may be identified. But only too often apparent changes in an encephalogram are diffuse and widespread involving the entire ventricular system, the whole subarachnoid space and basilar cisternæ. Are such slight differences in the air shadows due to lesions or to "normal abnormalities"?

However, failure to describe an encephalogram normal in every detail is hardly a valid criticism of this excellent monograph. The information the Reviewer demands will not be forthcoming until some enterprising soul carries out 500 encephalograms on patients with no clinical evidence of an intracranial lesion. Then and then only shall we have knowledge of a completely normal encephalogram and the normal variations which can occur without specific cause. And what a blessing such information will be to an honest witness in attempting to evaluate the medico-legal worth of many encephalograms.

The publishers of this monograph are to be congratulated on the excellence of the reproduction of the Roentgen ray films and on the nearly complete lack of typographical errors. An excellent bibliography is appended.

This monograph can be recommended unqualifiedly as a basis for the interpretation of encephalograms. Every radiologist, neurologist and neurosurgeon who has to read them should study it carefully. F. G.

HEART FAILURE. By ARTHUR M. FISHBERG, M.D., Associate in Medicine, Mount Sinai Hospital, New York City. Pp. 788; 25 illustrations. Philadelphia: Lea & Febiger, 1937. Price, \$8.50.

THE author states that his aim is to portray the advances in knowledge of the nature and treatment of circulatory failure, for the practising physician, in a fashion that will aid him in his daily work. The discussion is comprehensive and includes practically all aspects of circulatory failure, whether it originates in the heart or in the periphery. The literature has been carefully studied and utilized. The author has an excellent critical sense as well as an extensive knowledge of his subject and is able to distinguish between sound and unsound work. The book is unreservedly recommended to physicians who wish to bring their knowledge of the subject of circulatory failure up to date. C. W.

FAMILY CARE OF MENTAL PATIENTS. A Review of Systems of Family Care in America and Europe. Edited by HORATIO M. POLLOCK, PH.D., New York State Department of Mental Hygiene; with 5 Contributors. Pp. 247; 22 illustrations. Utica, N. Y.: State Hospital Press, 1936. Price, \$2.50.

THIS collaborated study of the systems employed in Europe and the United States tells of a neglected phase of psychiatry. Most of those suited to this care are mental patients, although some epileptics and feeble-minded can be farmed out; however, none may show violence, sex tendencies nor the urge to escape. The movement began at Gheel, Belgium in the

sixth century, where at present about half the town-families are hosts to some 3000 patients. The advantages to these colonists are home comfort, normal associations, greater freedom and work suited to their condition, some being self-supporting; to the foster families comes greater economic security; and since fewer institution buildings, with their expensive maintenance are required, the burden upon the taxpayer is lessened. In America, Massachusetts was pioneer in family care, with New York recently availing herself of its advantages. It is hoped that this country may see more and more mental patients cared for in homes.

N. Y.

THE CURE OF HIGH BLOOD PRESSURE BY RESPIRATORY EXERCISES. By **LOTHAR GOTTLIEB TIRALA, M.D., Ph.D.**, Professor of Medicine, University of Munich. Authorized Translation, by **FREDA DOUGLAS and ALBRECHT DOUGLAS, M.D., Ph.D.** Pp. 71; 11 illustrations and 2 colored plates. New York: B. Westermann Company, Inc., n.d. Price, \$1.25.

The author believes that in hypertension there is a state of chronic suffocation, the result of a decreased sensitivity of the respiratory center and consequent underventilation. The retained CO₂ as well as derivatives of ingested meat cause a stimulation of the vasoconstrictor center, bringing about hypertension. His treatment therefore stresses deep breathing exercises and a vegetable diet. Neither the argument nor the few illustrative case reports (less than a dozen) are convincing. The translation is as poor as the book.

R. K.

THE BIOLOGY OF HUMAN CONFLICT. An Anatomy of Behavior, Individual and Social. By **TRIGANT BURROW, M.D., Ph.D.**, Scientific Director, The Lifwynn Foundation, New York City. Pp. 435. New York: The Macmillan Company, 1937. Price, \$3.50.

ON Lake Chateaugay is Camp Lifwynn, where in a "normal asylum," a variant psychoanalyst and others work out their chosen problems. With a flair for doing unusual things, their leader, a "phyloanalyst," has established a laboratory for group-analysis, co-workers being lay and professional, normal and neurotic, male and female. Were it not for an informative glossary, this investigator would confound one with his Winchell-like urge for coining words.

Phyloanalysis (literally, not race-analysis but group-analysis) is concerned with the dissection of group-behavior disorders; a neurosis is regarded as an internal tensional affection enveloping mankind, and its correction calls for a "basic physiological reorientation of the total organism in relation to the total environment."

Psychoanalysis tends toward mysticism and its votaries are too dogmatic. But perhaps this writer is ahead of his time, a calamity that has overtaken others—Socrates, Bruno, Columbus, Bacon, Galileo. Further findings of this movement may be sponsored by the Foundation.

N. Y.

PHYSICIAN, PASTOR AND PATIENT. Problems in Pastoral Medicine. By **GEORGE W. JACOBY**, Past President of the American Neurological Association and the New York Neurological Society. Pp. 390; 20 illustrations. New York: Paul B. Hoeber, Inc., 1936. Price, \$3.50.

IN view of the lessening opportunities of the physician for a close personal relationship to his patients, the author points out that the physician can find in the clergyman a valuable ally in the handling of many medical and

social problems. He cites many ways in which religion in the past and present has directly influenced the health problems of mankind. He is interested in the religions of today insofar as they affect public health and physical well-being. "Faith and doctrine do not enter into discussion except when they bring physician and clergyman into harmony or conflict." The author deals with numerous practical problems, such as contraception and abortion, suicide, the divorce problem, crime, sterilization, sex education, euthanasia, in a calm and fair manner, with statements of opinions on these subjects as held by the adherents of various faiths. The book will be found interesting and useful by physicians and clergy alike.

R. K.

CANCER AND DIET. With Facts and Observations on Related Subjects. By FREDERICK L. HOFFMAN, LL.D., the Biochemical Research Foundation of the Franklin Institute, Philadelphia. Pp. 767; 187 tables and 8 charts. Baltimore: The Williams & Wilkins Company, 1937. Price, \$5.00.

THE material in this unique volume is considered under four separate headings: 1, Dietary Theories of Cancer; 2, The Modern Diet; 3, Cancer Metabolism; 4, Dietary Facts Concerning Cancer Patients. The discussion is exhaustive. While it is true that much of the material is worthless as scientific data, it helps one appreciate the long and tedious search that has gone before.

The evidence presented throughout the book is more or less conflicting. Almost every question involves contradictions and divergencies of opinion. One cannot help being amazed, however, at the quantity of data gathered for this analysis. Such items as race, religion, smoking, water, and vitamin intake, and their relation to cancer are meticulously presented.

We can think of nothing that might have added to the all-inclusive character of this review. Yet, in spite of the excellence of the presentation, we could not convince ourselves that diet was a dominating factor in cancer.

P. H.

A TEXTBOOK OF MEDICINE. By CHARLES PHILLIPS EMERSON, M.D., Research Professor of Medicine, Indiana University; Formerly Associate in Medicine and Medical Resident, Johns Hopkins University and Hospital, etc. Pp. 1296. Philadelphia: J. B. Lippincott Company, 1936. Price, \$8.00.

THIS new medical text has a number of interesting features. Chief of these is the author's aim to present Internal Medicine "in terms of the clinical pictures of diseases, and to explain these by the findings of pathology, biochemistry, and the other preclinical sciences, rather than to emphasize the latter." The author therefore portrays the syndrome which each disease presents, and, "lest they blur this, has added the contributions of the preclinical sciences (and more extensively than is the custom) in special paragraphs and footnotes." Another feature is the numerous historical references and the short biographies of many of the pathfinders in medicine. Emphasis is also placed on the personal factor in disease, including heredity, environment and the patient's biological and emotional reactions. The book, which is very well written, is obviously the product of a wise and seasoned clinician. It is open to less than average of the objections which so often apply to a textbook of medicine by a single author, who can obviously not be an authority on all phases of internal medicine and who is bound to have a few peculiarities of opinion. Thus one might criticize the understatement of the value of Roentgen rays in pulmonary tuberculosis;

the overcautious, at times antagonistic, attitude toward allergy and the denial of the possibility of an allergic factor in migraine (yet the book contains more and better information on allergy than do most one-volume textbooks of medicine); the failure to mention ergotamine tartrate in the treatment of the migranous paroxysm and prostigmine for myasthenia gravis. The typesetter slipped in an error by putting "severe" instead of "swine" before influenza in connection with Shope's work. All of these are points which can easily be taken care of in future editions. The fact remains, that the book reached a high standard of excellence and should be welcomed by teachers and students alike.

R. K.

EPIDEMIOLOGIE. Grundbegriffe und Ergebnisse. By PROF. DR. MED. ADOLF GOTTSTEIN, Ministerial-Direktor i. R., Berlin. Pp. 285; 16 figures. Wien: Franz Deuticke, 1937. Price, Paper, M. 15; Bound, M. 17.40.

THIS book has been written by an experienced worker who looks back on a long and successful career as an epidemiologist. There is a thorough discussion of the causes, courses and sequels of individual epidemics. However, the most valuable ingredient of the book appears to be a critical analysis to which the fundamental principles of epidemiology are subjected.

W. E.

THE INTERNATIONAL MEDICAL ANNUAL. Fifty-fifth Year, 1937. A Year-book of Treatment and Practitioner's Index. Thirty-four Contributors. Editors: H. LETHEBY TIDY, M.A., M.D. (OXON.), F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S. Pp. 605; 89 text illustrations and 68 plates (some in color). Baltimore: William Wood & Co., 1937. Price, \$6.00.

As usual, this annual presents an authoritative and reliable survey of recent progress in medicine—the word being interpreted in a wide sense. While great skill has been shown in condensing the huge material into usable form, the editors have wisely left the contributors free to select without insisting on the impossible element of comprehensiveness. Without in any way, then, replacing textbooks or periodicals on the wide field covered, this annual should be of great use to the practicing physician in keeping him up to date, and as a desk companion.

E. K.

THE TECHNIC OF LOCAL ANESTHESIA. By ARTHUR E. HERTZLER, A.M., M.D., Ph.D., LL.D., F.A.C.S., Professor of Surgery in the University of Kansas; Surgeon to the Halstead Hospital, Halstead, Kansas, etc. Pp. 284; 142 illustrations. Sixth Edition. St. Louis: The C. V. Mosby Company, 1937. Price, \$5.00.

THE sixth edition of Hertzler's book on local anesthesia has been changed very little from the fifth edition. Except for a few changes on spinal anesthesia and a few notations concerning the newer anesthetic drugs, the new edition has little to add over the previous one. The technique of local anesthesia is considered from the point of view of infiltration and local field block rather than regional or nerve block, so that the reader hunts in vain for the technique of the more complicated block, such as that of the brachial plexus. Anesthesia is described under regional sections and the book is well illustrated to show how the author induces his local anesthesia. The continued issuing of new editions of this work is a testimonial to its popularity.

L. F.

CONTRIBUTIONS TO THE MICROSCOPIC ANATOMY OF THE PANCREAS BY PAUL LANGERHANS [Berlin, 1869]. Reprint of the German Original with an English Translation and an Introductory Essay by H. MORRISON, M.D. Pp. 39; illustrated. Baltimore: The Johns Hopkins Press, 1937. Price, \$1.00.

AGAIN we are indebted to the Johns Hopkins Press for another interesting reprint of a medical classic. Morrison's Introductory Essay, list of publications, and three scarce photographs add to the value of this contribution to medical history. E. K.

MICROMETHODIK. Quantitative Bestimmung der Harn-, Blut- und Organbestandteile in kleinen Mengen für klinische und experimentelle Zwecke. By LUDWIG PINCUSSEN. Pp. 193; 31 illustrations. Sixth Edition. Leipzig: Franz Deuticke, 1937. Price, M. 5.

THIS manual describes procedures for the chemical analyses of the various components in the blood, urine, and other biological fluids such as may be presented to the biochemistry division of a hospital laboratory for analysis. For many of the analyses the author has selected and outlined only one method. Although the book mentions the principles upon which given analytical procedures are based, nevertheless, it contains very little critical evaluation of the methods. The bibliography is wholly unsatisfactory and the references, when given, are frequently incomplete. F. S.

THE PATIENT AND THE WEATHER. Vol. IV. Part 1. Organic Disease, Cardio-vascular-renal Disease. By WILLIAM F. PETERSEN, M.D. With the assistance of MARGARET E. MILLIKEN, S.M. Including a chapter on Experimental Endocarditis by ALEXANDER J. NEDZEL, M.D., Associate Professor in the Department of Pathology, Bacteriology and Public Health; University of Illinois, College of Medicine, Chicago. Pp. 663 (lithographed); 443 illustrations. Ann Arbor: Edwards Brothers, Inc., 1937. Price, \$10.00.

IN the preceding volumes, were introductory chapters that analyzed pertinent topics. Here, everyday clinical episodes as observed in case reports are given immediate attention, with the primary interest, not in the end result, but in the fact, "that organic disease may take its origin from subminimal environmental stimuli." In Chapter I, a bit of spoofing is indulged in at the expense of the author's surgical and psychoanalytical friends. Chapter II, discusses March episodes. Chapters III, IV, V and VI, consider diseases of the heart, vessels and kidneys. Chapter VII, endocarditis, with Section A, discussing clinical cases; in Section B, are submitted various case histories from the service of colleagues, wherefrom, deductions were such that the attempt experimentally to produce lesions was decided upon. The final chapter by Professor Nedzel, assays the data obtained through experimental production of bacterial endocarditis in dogs. Here, following pressor episodes and bacterial injections, typical valvular endocarditis was produced, more readily so during late winter and spring. With the artificial production of pressor episodes, an occasional typical endocarditis was observed, without bacterial injections. Therefore, it is concluded that the thesis proposed by Petersen is experimentally demonstrable. Throughout the volume the research work is so intricate that it can only be appreciated by specialists. The bibliography is noteworthily extensive. N. Y.

PHYSICIANS AND MEDICAL CARE. By ESTHER LUCILE BROWN, Department of Statistics, Russell Sage Foundation. Pp. 202. New York: Russell Sage Foundation, 1937. Price, 75c.

The changes in the relation of medicine to society are taking place so rapidly and in so many ways that it is difficult for the members of the profession to realize their extent and significance. Therefore this book should have particular interest to those who wish to understand the present status of medicine and its changing position as a unit of our complex social structure. It indicates the modern trends and social forces affecting medical care and their influence on the profession.

The book is based on the more important literature which has recently appeared related to medical education and medical care, and is a fair-minded, clear summary of these voluminous writings which should be welcomed by the members of the profession who wish to know what is taking place in the American medical profession. It should also be of especial interest to those contemplating the study of medicine.

The problems of medical education are first discussed, followed by an account of the national organizations which guide and control the profession from within. The latter half of the book discusses the number of physicians and the demand for their services, the distribution of physicians and their incomes, new forms of medical service and finally the fundamental problem of adequate medical care for all the people. It is pointed out that serious difficulties confront those who seek to devise means for extending medical care to the entire population while still preserving all that is best in medicine, and the author indicates what these difficulties are. During the past few decades the problem in this country has been the improvement of medical education and the development of the basic sciences of medicine, while today the urgent problem "is that of devising ways and means whereby adequate care can be provided for the entire population and physicians compensated fairly for the service rendered." As this is primarily an economic problem involving both physicians and society in general, it is desirable for physicians to understand the demands of society upon medicine and for the laity to comprehend the needs, structure and functions of the medical profession.

This book should serve a useful purpose in stimulating a mutual understanding between the medical profession and the public, and the author is to be congratulated upon the presentation of a clear, concise and very interesting account of the present status of the medical profession in relation to the problem of the provision of medical care.

G. R.

MATERNAL CARE. The Principles of Antepartum, Intrapartum, and Postpartum Care for the Practitioner of Obstetrics. Approved by The American Committee on Maternal Welfare, Inc. Prepared by Drs. W. C. DANFORTH, G. W. KOSMAK, R. L. DE NORMANDIE and F. L. ADAIR. DR. FRED. L. ADAIR, Editor. Pp. 93. Chicago: The University of Chicago Press, 1937. Price, \$1.00.

The widespread campaign for the improvement of Maternal Care showed a need for the concise statement of the principles of antepartum, intrapartum and postpartum care. It is felt that this handbook will amply supply the needs of the average practitioner of obstetrics. The material is simply and directly presented with emphasis on the cardinal principles and insistence on the nearest approach to asepsis which is possible and a short and direct discussion of obstetric operations and complications. It is hoped that the book will have a wide distribution among general practitioners, hospital interns, and public health nurses.

P. W.

INFANTILE PARALYSIS AND CEREBRAL DIPLEGIA. Methods Used for the Restoration of Function. By ELIZABETH KENNY. With a Foreword by HERBERT J. WILKINSON, Professor of Anatomy and Dean of the Faculty of Medicine, University of Queensland. Pp. 125; 51 illustrations. Sidney, Australia: Angus & Robertson, Limited, 1937. Price, £ 1/1/-

This offering is of Sister Kenny's 16 years scientific work with patients, always under the care of medical men, wherein improvement was brought about in abandoned paralytics, some of 20 or 30 years standing; and more rapid improvement in early subjects, in whom active or passive movements of the joints, were made sometimes from the beginning. Patients were treated individually and alone; the position assumed was that most favorable to concentration, after which the subject was taught to visualize the area where muscle movements were expected. Believing she has a mission this woman endowed with an exceptional personality, boundless optimism and great physical energy, has been able to get some surprisingly brilliant results. Criticism is of neglecting to employ other useful methods such as massage and immobilization, which latter is for the most part condemned.

N. Y.

FISCHERISMS. Being a sheaf of sundry and divers utterances culled from the lectures of MARTIN H. FISCHER, Professor of Physiology in the University of Cincinnati. By HOWARD FABING. Pp. 47; 1 illustration. A Second and Enlarged Edition by Ray Marr. Springfield, Ill.: Charles C Thomas, 1937. Price, \$1.50.

A PRIVATE print for Dr. Martin Fischer's students, this little anthology of aphorisms is, as stated on the cover, not for general circulation. Nevertheless, these asides from lectures on physiology contain not a few nuggets that are worth preservation as well as serving Cincinnati graduates as a "reminder of pleasant days gone by." The medical aphorism, as old as Hippocrates, has its appropriateness in these pithy, disjointed days, but also its limitations. As might be expected from a compilation of jottings from student note book margins, the levels vary greatly, nor are all the statements true or to be accepted—in some cases even the meaning is obscured by the synecopated form. However, many homely truths—piquantly expressed—may be found here applied to politics, philosophy and religion, as well as to all branches of medicine.

E. K.

A TEXTBOOK OF SURGICAL NURSING. By HENRY S. BROOKES, JR., M.D., Instructor in Clinical Surgery, Washington University School of Medicine; Surgeon to the Outpatients, Washington University Dispensary; Assistant Surgeon to Barnes Hospital. Pp. 636; 233 illustrations. St. Louis: The C. V. Mosby Company, 1937. Price, \$3.50.

THE author, in conjunction with several nursing supervisors at the Barnes Hospital, has compiled a book of nursing for surgical nurses which describes fairly closely the procedures as followed at that hospital.

The book gives a short introduction describing inflammations and infections, wounds, bandages, first aid, pre- and postoperative care and, very briefly, anesthesia. The section on the operating room is good. The instrument set-ups for various operations are given in detail and one of the especially interesting parts of the book are the illustrations with names of the instruments used in various operations. There are sections on regional surgery and finally a chapter on postoperative complications and one describing the various procedures such as catheterization, intravenous glucose, etc. At the end is appended a glossary of words used in surgery, which are defined in relatively simple terms.

The book is well illustrated throughout. Many of the illustrations have been borrowed from the works of other authors and some of them, as for

instance the illustration on page 113, have lost a great deal of their sharpness in reproduction so that it is very difficult to see what is described in the plate.

If there is any criticism to be offered of the book it is that there is relatively little concerning the nursing care of surgical patients. Too much emphasis has been placed on the surgical procedures themselves so that the book is more suitable as an introduction to surgery for medical students than as a reference or textbook for nurses, whose education neither fits them nor whose duty makes it necessary for them to follow in intricate detail the technique of surgical operations.

L. F.

PUBLIC MEDICAL SERVICES. A Survey of Tax-supported Medical Care in the United States. By MICHAEL M. DAVIS. Pp. 170. Chicago: The University of Chicago Press, 1937. Price \$1.50.

IN the discussion of medical care in this country which is so active today, the term "state medicine" is frequently heard. It is sometimes called erroneously "socialized medicine," and is seldom defined by those who advocate or condemn its adoption as a solution for the problems of medical care. Although everyone who speaks of state medicine has in mind medical care furnished by the government and therefore supported by taxation, few have stopped to say whether the term includes all medical care, curative as well as preventive, or whether it applies only to certain medical functions and to certain groups of people. Does state medicine mean that government shall actually control medical service, or only help to pay for the needed medical care which individuals cannot or will not pay for?

Before anyone makes public utterances about the dangers and demoralization of state medicine or advocates it as a panacea, he should know its present status in this country, how it has developed, what medical services are now tax-supported and what its future is likely to be, as judged by the evolutionary processes now going on which are extending the scope of state medicine.

Michael Davis gives a clear and authoritative account of this subject. His book is an expansion and modification of the section on public medical services which he contributed to the report on health security, prepared for President Roosevelt's Committee on Economic Security in 1934. The first part of the book gives an account of the kinds and extent of medical service which are now supported by taxation in this country. The subject is described under such headings as: home medical care; hospitals for acute and chronic diseases; hospitals and clinics for mental disease and tuberculosis; tax payments to non-governmental hospitals; general medical care for certain non-dependent groups for whom special responsibility is assumed by a government agency; medical care for diseases or conditions of public health interest.

The second part of the book consists of Summary and Comments, emphasis being laid on quality of service and coordination of service. Evidence is presented which shows that over a quarter of the medical care furnished to wage-earners and other people with small or no incomes, constituting 85% of the population, is tax-supported at the present time.

The author emphasizes the importance of maintaining personal understanding and confidence between physician and patient as a fundamental element of effective medical service, and he points out that the medical profession must give intellectual effort to the dispassionate solution of the problems of professional service. The author also puts his finger on some problems of medicine requiring coöperation of service for their solution which should be given careful consideration by the profession.

Michael Davis is one of the best informed and most experienced students of American Medicine, as a service and as a profession. Although outside

of the profession, he has been integrated with it as an administrator for so many years that he may now be said to be one of our most valuable medical statesmen. His study of Public Medical Services is a clear and useful contribution to the knowledge which is beginning to answer some of the controversial questions regarding the medical care of the American people.

G. R.

AUTONOMIC NEURO-EFFECTOR SYSTEMS. By WALTER B. CANNON, George Higginson Professor of Physiology, Harvard University, and ARTURO ROSENBLUETH, Assistant Professor of Physiology, Harvard University. Pp. 229; 42 illustrations. New York: The Macmillan Company, 1937. Price, \$4.00.

THIS monograph deals with "recently acquired evidence regarding the chemical step which intervenes between the nerve impulse and the effector in the functioning of the autonomic nervous system—not only the processes in the junctional region but also those occurring in the effectors themselves" (quotation from the authors' preface). It begins with a general consideration of the structure and functions of the autonomic nervous system, takes up some pertinent details of the finer innervation of smooth muscle, heart muscle, and glands, and proceeds to sketch the development of the current conception of transmission of nerve impulses by chemical agents liberated by the impulses—the so-called "cholinergic" and "adrenergic" conceptions; the first three chapters cover these points. Two chapters are then devoted to the parasympathomimetic substance (acetyl choline). The remaining nine chapters deal for the most part with the sympathomimetic substance ("sympathin") and with drug actions which bear upon it. The bibliography comprises 344 titles.

For the physician or biologist who desires a compact summary of reasons for believing that nerve impulses may be chemically transmitted, and a glimpse of some of the current conceptions of the ways in which chemical agents act upon living tissues so as to modify their function, this book is recommended most highly. Like nearly all recent monographs on this subject, this one makes the case for humoral transmission as strong as possible and the story is an extremely attractive one. Unlike the others, this one devotes more attention to "sympathin" than to acetyl choline; this is eminently fitting because the authors have done much more experimentation with the former than with the latter. Unfortunately "sympathin," being a substance of unknown composition (as the authors are careful to state), cannot be handled with the precision which has characterized the recent experiments made by Dale and his co-workers with acetyl choline; this precision furnishes the most potent argument in favor of humoral transmission, and one might expect the authors to include more of the cholinergic story for that reason, if for no other. Although the authors state (p. 123) that electrical phenomena in smooth muscle may be concomitants, not necessary links, in the excitatory chain, and that (p. 157) "sympathin" may be liberated in intimate relation to the reacting substance and this nerve stimulation may be effective after piperidinomethylbenzodioxane ("933 F") though a physiologically similar agent (adrenalin) injected into the blood is ineffective, they do not mention the converse possibility, namely that the liberation of "sympathin" may be only an incident in the excitatory process and the substance which reaches the blood stream may have had nothing to do with the physiologic effects of sympathetic nerve stimulation. The subject of humoral transmission of nerve impulses has developed too rapidly to permit impartial evaluation. Perhaps a few years hence the authors will revise or rewrite this monograph; comparison of the second edition with the first will be extremely interesting.

C. S.

HANDBOOK OF ORTHOPÆDIC SURGERY. By ALFRED RIVES SHANDS, JR., B.A., M.D., Associate Professor of Surgery in Charge of Orthopædic Surgery, Duke University School of Medicine, and Chief of the Orthopædic Service, Duke Hospital, Durham, N. C., etc. In Collaboration with RICHARD BEVERLY RANEY, B.A., M.D., Instructor in Orthopædic Surgery, Duke University, School of Medicine. Pp. 593; 169 illustrations. St. Louis: The C. V. Mosby Company, 1937. Price, \$5.00.

DR. SHANDS in his "Handbook of Orthopædic Surgery" has presented the subject in a very clear and concise manner. It is easy to read, and the reader is not lost or confused by long statistical reports. The book is unique in that not only the author's opinion is expressed, but also that of many other leading orthopædic surgeons on the various subjects under discussion. The author has presented the fundamentals of Orthopædic Surgery, paying particular attention to diagnosis and treatment.

There are 169 illustrations, very well done, which help the reader to visualize their characteristic features.

The bibliography is carefully indexed and most complete, which should be of immense value to both students and practitioners of medicine inasmuch as the references include leading American and English authors.

T. O.

NEW BOOKS.

Human Understanding and Its World. A Study of Societies. By K. W. MONSARRAT, Consulting Surgeon, Northern Hospital, Limerick; Formerly Dean of the Faculty of Medicine, University of Liverpool. Pp. 480; 42 figures. Liverpool: The University Press; London: Hodder & Stoughton, Ltd., 1937. Price, 15/-.

Russian Medicine. (Vol. XX of *Clio Medica*). By W. HORSLEY GANTT, M.D., Johns Hopkins University School of Medicine; Formerly Chief of Medical Division, American Relief Administration, Leningrad Unit (1922-1923); Collaborator in Pavlov's Laboratories (1925-1929). Pp. 214; 12 illustrations. New York: Paul B. Hoeber, Inc., 1937. Price, \$2.50.

Practical Talks on Kidney Disease. By EDWARD WEISS, M.D., Professor of Clinical Medicine, Temple University School of Medicine, Philadelphia. Pp. 176; illustrated. Springfield, Ill.: Charles C Thomas, 1937. Price, \$3.00.

Atlas of Hematology. By EDWIN E. OSGOOD, M.A., M.D., Assistant Professor of Medicine and Head of Experimental Medicine, University of Oregon Medical School, Portland, and CLARICE M. ASHWORTH, Medical Illustrator, University of Oregon Medical School, Portland. Pp. 255; 325 illustrations and frontispiece, all in full color. San Francisco: J. W. Stacey, Inc., 1937. Price, \$10.00.

A Text-book of Medical Bacteriology. By R. W. FAIRBROTHER, D.Sc., M.D., M.R.C.P., Lecturer in Bacteriology, University of Manchester; Late Research Fellow in Bacteriology, Lister Institute, London. Pp. 437; 12 illustrations and 32 tables. St. Louis: The C. V. Mosby Company, 1937. Price, \$4.50.

Family Care of Mental Patients. A Review of Systems of Family Care in America and Europe. Edited by HORATIO M. POLLOCK, Ph.D., New York State Department of Mental Hygiene, Albany, N. Y. Contributors: EDGAR A. DOLL, Ph.D., The Training School at Vineland, N. J.; HARRY A. LABURT, M.D., Harlem Valley State Hospital, Wingdale, N. Y.; PHILIP SMITH, M.D., New York State Department of Mental Hygiene, New York City; CHARLES E. THOMPSON, M.D., Gardner State Hospital, East Gardner, Mass.; CHARLES L. VAUX, M.D., Newark State School, Newark, N. J. Pp. 247; illustrated. Utica, N. Y.: State Hospitals Press, 1936. Price, \$2.50. (For Review, see p. 715.)

Syphilis. The Next Great Plague to Go. By MORRIS FISHBEIN, M.D. Pp. 70; illustrated. Philadelphia: David McKay Company, 1937. Price, \$1.00.

The British Encyclopædia of Medical Practice. Volume 4. Diarrhœa to Endoscopy of the Rectum. Under the General Editorship of SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge, etc. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., G. GREY TURNER, D.Ch., M.S., F.R.C.S., JAMES YOUNG, D.S.O., M.D., F.R.C.S. ED., F.C.O.G., SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S. and F. M. R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 650; 129 illustrations. London: Butterworth & Co. (Publishers), Ltd., 1937. Price, \$12.00.

Clinical Urinalysis and Its Interpretation. By ROBERT A. KILDUFFE, A.M., M.D., F.A.S.C.P., Director of Laboratories, Atlantic City Hospital; Pathologist, Atlantic County Hospital for Tuberculous Diseases; Serologist, County Hospital for Mental Diseases; City Bacteriologist, City of Atlantic City, etc. Pp. 428; 40 illustrations. Philadelphia: F. A. Davis Company, 1937.

Le Anemie Emolitiche Costituzionali Ereditarie. By DR. GIULIO MOMIGLIANO-LEVI. Pp. 108; 16 illustrations. Torino: Edizioni Minerva Medica, S. A., 1937. (Price not given.)

An Epiphyseal Chart. (Reprinted from an article published in The American Journal of Roentgenology and Radium Therapy, Vol. 30, No. 6, December, 1933.) By PAUL C. HODGES, Ph.D., M.D., Division of Roentgenology, University of Chicago. Chicago: The University of Chicago Press, 1937. Price, 25c.

This chart makes available at a glance the developmental history of the bones of the human skeleton from fetal life to maturity. P.H.

International Clinics, Vol. III, Forty-seventh Series, 1937. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 13 collaborators. Pp. 328; illustrated. Philadelphia: J. B. Lippincott Company, 1937.

This volume is made up of 24 articles covering many phases of medicine. It has an unusually distinguished list of contributors from several states but none from abroad. Conspicuous are the 9 articles from the Johns Hopkins Hospital.

Erbkrankheit und Fertilität. Mikropathologie der Spermien erbkranker Männer. By DR. med. et med. vet. H. STIASNY, Assistent der chirurgischen Abteilung des städtischen Krankenhauses "Am Urban," Berlin, and DR. med. K. D. J. GENERALES, JR., Lowell, Mass., z. Zt. Volontär-assistent der chirurgischen Abteilung des städtischen Krankenhauses "Am Urban," Berlin. Mit einem Geleitwort von PROF. DR. ERWIN GOHRBANDT. Pp. 163; 60 illustrations; 21 tables (16 in colors). Stuttgart: Ferdinand Enke, 1937. Price, Paper, Rm. 27.; Bound, Rm. 29.

Heilkunde und Volkstum auf Bali. By DR. med. WOLFGANG WECK, ehem. Hoofd-Gouvernementsarzt in Niederländisch-Indien. Pp. 248; 27 illustrations. Stuttgart: Ferdinand Enke, 1937. Price, Paper, Rm. 19; Bound, Rm. 20.60.

Recent Advances in Industrial Hygiene and Medicine. By T. M. LING, M.A., B.M. (Oxon.), M.R.C.P. (Lond.), Senior Medical Officer, Bristol Police, etc. Foreword by J. A. NIXON, C.M.G., M.D., F.R.C.P., Emeritus Professor of Medicine, University of Bristol, etc. Pp. 212; 29 illustrations. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, \$3.50.

The Patient and the Weather, Vol. IV, Part 2. Organic Disease. Hypo- and Hyperthyroidism, Diabetes, The Blood Dyscrasias, Tuberculosis. By WILLIAM F. PETERSEN, M.D., with the assistance of MARGARET E. MILLIKEN, S. M. Pp. 729 (lithoprinted); 380 illustrations. Ann Arbor: Edwards Brothers, Inc., 1937. Price, \$11.00.

Injection Treatment of Hernia. By CARL O. RICE, M.D., F.A.C.S., Instructor in Surgery, University of Minnesota School of Medicine; Surgeon in Charge of the Surgical Out-Patient Department of Minneapolis General Hospital, etc. With the assistance and coöperation of HAMLIN MATTSON, M.D. Pp. 266; 83 illustrations. Philadelphia: F. A. Davis Company, 1937. Price, \$4.50.

NEW EDITIONS.

Recent Advances in Pulmonary Tuberculosis. By L. S. T. BURRELL, M.A., M.D. (CANTAB.), F.R.C.P. (LOND.), Senior Physician to Royal Free Hospital; Physician to Brompton Hospital for Consumption and Diseases of the Chest, etc. Pp. 320; 22 text figures and 48 plates. Third Edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, \$5.00.

Clinical Electrocardiography. By SIR THOMAS LEWIS, M.D., F.R.S., D.Sc., LL.D., F.R.C.P., C.B.E., Physician in charge of Department of Clinical Research, University College Hospital, etc. Pp. 128; 109 illustrations. Sixth Edition. London: Shaw & Sons Ltd., 1937. Price, 8s. 6d.

The continued popularity of this excellent little book and its reasonable price are ample explanations of the frequent editions that have appeared.

A Textbook of Histology. By HARVEY ERNEST JORDAN, A.M., PH.D., Professor of Histology and Embryology, University of Virginia. Pp. 738; 610 illustrations (many in color). Seventh Edition. New York: D. Appleton-Century Company, Inc., 1937. Price, \$7.50.

Textual changes, not lengthy, chiefly concern the periosteum, ovaries, suprarenals, thymus and pineal. Thirty-nine illustrations have been replaced; it is to be hoped that many more of the antique figures will be replaced in future editions.

Diseases of the Heart. Described for Practitioners and Students. By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., Physician in charge of Department of Clinical Research, University College Hospital, London; Honorary Consulting Physician to the Ministry of Pensions, etc. Pp. 297; 45 illustrations. New York: The Macmillan Company, 1937. Price, \$3.50.

The virtues and defects noticed in the Review (*Am. J. Med. Sci.*, 186, 439, 1933) of the first edition of this book are found unchanged in the present edition. According to the author, the text has been thoroughly revised "and all recent and relevant advances in our knowledge which it is judged will prove of value to practitioners, have been incorporated." Leaving aside the questionable punctuations, we doubt if this statement can be taken literally.

The Human Body. By LOGAN CLENDENING, M.D. Pp. 452; 106 illustrations by W. C. SHEPARD and DALE BERONIUS and from photographs. Third edition, corrected, enlarged and rewritten. New York: Alfred A. Knopf, Inc., 1937. Price, \$3.75.

A Textbook of the Practice of Medicine. By Various Authors. Edited by FREDERICK W. PRICE, M.D., C.M., F.R.C.P., F.R.S. (EDIN.), Consulting Physician to the Royal Northern Hospital; Senior Physician to the National Hospital for Diseases of the Heart, London, etc. Pp. 2038; 112 illustrations. Fifth Edition. New York: Oxford University Press, 1937. Price, \$12.50.

A Textbook of Medicine. By American Authors. Edited by RUSSELL L. CECIL, A.B., M.D., Sc.D., Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital, New York City. Associate Editor for Diseases of the Nervous System, FOSTER KENNEDY, M.D., F.R.S.E., Professor of Neurology, Cornell University Medical College; Director, Department of Neurology, Bellevue Hospital, New York City. Pp. 1614; 42 illustrations. Fourth Edition, revised and entirely reset. Philadelphia: W. B. Saunders Company, 1937. Price, \$9.00.

PROGRESS OF MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

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INSULIN.

THE number of publications during the past 5 years concerning insulin has been so large that it would be almost impossible to review all the material in print. Literally, thousands of papers dealing with insulin from one or another viewpoint have appeared, and it is obvious that some limitations had to be decided upon in a review of this type. We have chosen, therefore, to present the subject—insulin—from two viewpoints: (1) the increase in the therapeutic range of the hormone, and (2) the recent developments of various insulin retards.

The Use of Insulin in Non-diabetic Conditions. Even though insulin was originally intended as a chief remedial measure for diabetes mellitus, it has been used for almost every pathologic entity and ailment to which human flesh is heir. This increase in the therapeutic range of insulin in non-diabetic states is even more remarkable since there is no sound physiologic or pharmacologic basis for its use. Yet, on purely empiric grounds insulin has been used in the treatment of: 1, diseases of the lungs;^{2a,b,8,64,71} 2, heart;^{22,38,43,46,60,75} 3, kidneys;^{10,53} 4, gastro-intestinal disorders;^{21,24,34,36,67,77,86} 5, pernicious anemia;¹¹ 6, diseases of the joints;^{15,19} 7, in cases of simple undernutrition;^{13,31,56} 8, in obliterative vascular diseases;^{10,19} 9, in menstrual disorders;^{4,42,50} 10, in diseases of the skin;^{80,87} 11, allergic states;^{53a,b} 12, in drug addiction;^{18,57,66} 13, in hepatic disorders;^{12,16,51,82} 14, in various psychoses, chiefly schizophrenia;^{27,68,74,79,87} 15, in neurologic conditions;⁵⁸ 16, to stimulate sexual development;⁵⁵ 17, in the study of experimental tumors;⁴⁵ 18, and even in the treatment of hyperinsulinism itself.³⁵ Such an extensive use of the hormone is most remarkable since excellent therapeutic results have been reported in *all* the pathologic entities treated. A careful study of these data reveals that many of the abnormalities treated often recover spontaneously and, therefore, the therapeutic usefulness of insulin in such instances is open to question.

Furthermore, many reports deal with a single case, or a small series of cases, and such reports are not very convincing. There are, however, non-diabetic states in which insulin has been used with results reported so startling as to warrant some detailed comment. The series of cases presented have been large, and the conditions reported as most benefited may be divided into three groups: 1, simple undernutrition; 2, pulmonary tuberculosis; 3, the psychoses—chiefly schizophrenias.

Insulin in Simple Undernutrition. It is now well established that insulin can be used to increase the weight of thin but otherwise healthy subjects. The therapeutic principle is based on the fact that mild hypoglycemia induces hunger, and stimulates the appetite, thus causing the individual to eat more. It is obvious that in any person, if all other factors are unaltered and the food consumption increased, that a gain in weight must result. The method usually employed was to administer 10 units of insulin about 3 times a day about $\frac{1}{2}$ hour before meals. The diet was liberal. The individual injections were increased in number or dosage until a satisfactory result was obtained. All observers report gains in weight. Himwich and Nahum³¹ gave their patients 3 units of insulin every 3 hours increasing gradually to 10 or more units. They treated 4 patients and reported such gains as 22½ lbs. in 23 days and 15 lbs. in 39 days. Metz,⁶⁶ using larger doses of 20 to 30 units 3 times a day, reported weight increases of 15 to 25 lbs. Blotner,^{13a b c} who has probably had the greatest experience with this method of treatment, stated that the use of insulin to produce gain in weight in certain undernourished cases is "reasonable, uncomplicated and a practical method of treatment." In a series of 79 thin, healthy adults, Blotner reported an immediate and rapid gain in weight on 10 units 3 times daily. By tissue studies he demonstrated that the gain in weight was due not to water retention, but to actual deposit of fat.

It must be remembered that while unanimity of opinion exists, that an individual can be made fat as long as proper doses of insulin are given, not every one is in accord as to what happens to such persons once insulin is discontinued. This is an important consideration before recommending this form of treatment. Not all thin individuals can be "made fat" permanently. Some of them are thin by heredity. Their appetite is excellent and their caloric intake exceeds their calculated requirements. Their basal metabolic rate is within normal limits. Yet, in spite of all such normal factors and a liberal diet they fail to gain weight. It is certainly quite possible to make them gain by means of insulin. But, when insulin is discontinued, their weight gradually falls to its original level.

Insulin in Tuberculosis. Probably the largest series of cases of pulmonary tuberculosis treated with insulin was published by Allen, Douglas, Warren and Pottenger.³ They treated 134 cases of all grades of severity, and whenever good therapeutic effects were demonstrable, the improvement was not in the tuberculosis but in the nutrition of the patient. Insulin proved of value in the cases of pulmonary tuberculosis in combating such symptoms as anorexia and serious malnutrition. A gain in weight as well as strength, an improvement in well-being and spirits were conspicuous advantages of the treatment. The authors admit that in the most severe cases insulin is useless; but as there are no contraindications, it may be worth while giving this form of therapy

a trial. Allen² and his associates state that insulin is of value not only because of its effect on appetite, but because it may alter defects in the metabolism of carbohydrate, which they found to be present in 40% of 128 patients with pulmonary tuberculosis. Abnormal glucose tolerance curves were found in these patients. Spellberg and Rosenblum,⁷⁶ using insulin in 13 cases of far-advanced pulmonary tuberculosis, stated that all of the patients showed improvement in appetite and gastric symptoms; 1 patient gained as much as 24 lbs. These authors did not claim that insulin was a specific cure for pulmonary tuberculosis, but it was their opinion that it helped by improving gastric motility, secretion and storage of glycogen in the liver and of fat subcutaneously. Banyai and Jurgens⁸ studied the effect of insulin in 43 non-diabetic patients with active, moderately- and far-advanced pulmonary tuberculosis. Insulin was of value in that it improved the appetite in 19 (79%) of the 24 moderately-advanced cases and in 11 (57%) of the 19 far-advanced cases. The weight was increased in 54% of the moderately-advanced and 47% of the far-advanced cases. The above three reports are representative of the conclusions in connection with the use of insulin in non-diabetic pulmonary tuberculosis. It is apparent that its chief virtue lies in its ability to stimulate the appetite and increase the patient's weight. Insulin is not a "cure" for tuberculosis. The evidence that the use of insulin in tuberculosis is justifiable, because of a disturbance of carbohydrate metabolism, as evidenced by abnormal glucose tolerance curves is not convincing, as almost any infectious process as well as starvation will under certain conditions produce abnormal glucose tolerance curves. From the data given and from groups of smaller series of cases it is clear that whatever virtue insulin may have in the treatment of non-diabetic tuberculosis, it has no direct effect on the tuberculosis itself. Its great therapeutic value lies in its ability to stimulate the appetite thereby increasing the weight of the patient just as it does in cases of simple undernutrition.

Insulin in the Treatment of Schizophrenia. About 4 years ago, Sakel,^{66b} of Vienna, reported a new method of treating psychoses, based upon the induction of hypoglycemic coma by means of large doses of insulin. His results, particularly for the treatment of schizophrenia, were so encouraging that numerous investigators have adopted it, and, as a result, in a short period of time there are available in the literature hundreds of case reports showing the benefits from the use of insulin in a condition that has always been regarded as practically hopeless.

The history leading up to the use of large, shock-producing doses of insulin is interesting. Insulin was first used by many^{27a, b, c, 66a, b, 74, 79, 87b, c, d} in cases of mental diseases as a means of improving appetite and nutrition. But, in the course of such therapy, Strecker⁷⁹ noted improvement among some disturbed patients after an unexpected insulin reaction. Mebel⁸⁷ and, at about the same time, Jacob and Doussinet⁸⁷ reported cures in psychotic patients to whom large doses of insulin were given. Other favorable results were being published from various clinics, but the specificity of insulin as the effective agent was not particularly emphasized, until Sakel presented his results. This investigator was the first to advocate the use of shock-producing doses of insulin for the treatment of schizophrenia. Following his reports abroad, Glueck,^{27a, b, c} Wortis^{87b, c, d} and others in this country have treated schizophrenic

patients with insulin and they have publicly stated that the method has promise. Sakel has personally treated over 300 cases, and, although the evaluation of the results is difficult because of spontaneous remissions which occur in schizophrenia, yet in the first 100 cases he has had 88% "good or full remissions." These patients could resume their work. Since spontaneous remissions occur in only 5 to 20 % of the cases, it is obvious that treatment with insulin offers considerable hope. Sakel induced hypoglycemic coma by varying doses of insulin. He stated that the management of the coma so induced is much more important than its production, as the therapeutic results depend upon the proper termination of the hypoglycemic coma. As yet, he has not evolved any criteria by which one can judge when the hypoglycemia should be terminated. This was usually done by administering glucose by stomach tube or intravenously. Occasionally, though rarely, adrenalin had to be given. To quote Sakel:^{56b,c} "When the treatment first developed I could not say exactly why I terminated the hypoglycemia at one point in one case and at a different point in another case, or why I should vary the period of hypoglycemia in the same case in different stages of treatment. The probability was that I was guided by dim unconscious recollections of previous experiences in similar cases." Sakel at first was of the opinion that only the early cases should be treated, but after his experience with over 300 cases he felt that some chronic cases may also benefit from this type of treatment. Glueck,^{27a,b,c} who has had experience with this method, also remarks that the technique cannot be readily standardized. Wortis,^{87b,c,d} reporting on 13 cases, stated that 9 have "definitely benefited from the treatment and 4 have so far been unresponsive." He recorded the interesting observation that a hypoglycemic reaction will usually follow a similar pattern every time a hypoglycemic state is induced. This fact has been observed among diabetic patients in whom successive reactions occurred because of excessive doses of insulin.

Smith⁷⁴ felt that, in view of the beneficial results reported in the treatment of the psychoses, insulin therapy might be applicable to "at least some neuroses," and after treating 8 cases he stated that "insulin therapy proved effectual in treating both psychotic and psychoneurotic patients."

Because of such dramatic reports, dealing with hundreds of cases, it is not difficult to understand the enthusiastic and hopeful reception this method of therapy has to date enjoyed. It has been widely publicized in the lay and medical press. There is no doubt that it merits much consideration, as there is no medical treatment for schizophrenia and psychotherapy has not been encouraging. Yet, there still remains a large group of conservative physicians who advise extreme caution before accepting insulin as a specific for schizophrenia.²⁰ It is to be emphasized that there is nothing specific either pharmacologically or physiologically to support the use of insulin in the treatment of the psychoses. Perhaps the published results justify such a procedure on an empiric basis, because it offers some tangible method of therapy for a condition for which no other treatment is known. Yet, if accepted, it must be employed with considerable caution until its mechanism is understood and a relatively standardized, rather than an intuitive technique, for its application is developed.

Insulin "Retards."* If it is assumed that diabetes mellitus is due to a defect in the insulin producing mechanism, then the artificial administration of this hormone should in a way compensate for such a deficiency. As a matter of fact it does. This dietum, therefore, may be stated without reservation—*Insulin benefits all patients presenting a group of symptoms or syndrome known as diabetes mellitus.* That it is only a substitution therapy is also well established. Some cases of diabetes need a smaller and others a larger amount of insulin to restore the metabolism of carbohydrate, at least approximately to a physiologic state. Since insulin is effective only when given parenterally, it is obvious that in the severe cases either *more* insulin will have to be given at one time or more frequent doses throughout the day. Both experimental and clinical experience have demonstrated that frequent small doses are much more effective as aids in the utilization and storage of carbohydrate, than the same quantity given at one time. In practice, therefore, it is the routine to administer 3 or 4 injections of insulin to the severe diabetic. Three are given 20 to 45 minutes before meals and the fourth either at bedtime or during the night. The criteria of satisfactory therapy, from the laboratory viewpoint, have been a sugar-free urine and a blood sugar curve approximating the normal configuration. Such desiderata were not always attainable as there were patients whose blood sugar would fluctuate from the hyperglycemic to the hypoglycemic level with the result that the patient would be on the verge of ketosis at one time and insulin shock, or even hypoglycemic coma at another. It was felt that these profound fluctuations were due to the rapidity of action of the administered insulin. The obvious approach to this problem, therefore, was to *slow up or retard* the action of insulin. If insulin could be so altered as to render its action slower, then the precipitous fall of the blood sugar and presumably its disagreeable symptoms, could be avoided. Since most investigators were of the opinion that the rapidity of action was due principally to the fact that insulin was rapidly absorbed, methods were sought to slow down its absorption. That is the cardinal principle of all slow acting insulin preparations.

A. Lipoids. There have been attempts to retard the action of insulin by mixing it with oils, cholesterol, lecithin, or combinations of the three. Leyton⁴⁹ used lecithin and various oils and felt that the insulin was more slowly absorbed when mixed with oil. Skouge and Sehrumpf⁷² presented evidence based on animal experiments and normal men that lecithin acted as a retard. They found that the blood sugar fell more slowly with the insulin-lecithin compound. Recently, Katseh, Scholderer, and Klatt⁴¹ have compounded a viscous insulin preparation which they have called "insulin durant." The character of the base used was not fully described, but from some of its properties it may be assumed to be lipid. They have used this product in 23 cases, and they were able to get along with *one* injection every 2 or 3 days instead of 3 injections daily. The material is injected intramuscularly and because of its marked viscosity it is put up into carpules which have rubber caps at both ends. The carpule is then placed into a metal syringe,

* Retard is a substance which slows the pharmacologic action of the product with which it has been mixed.

from which the injection is made. With this compound they gave as much as 330 units of insulin at one time.

In general, the use of oils as retards has not been adopted. The results were not sharp and an additional drawback was the local reaction—pain and swelling. The “insulin durant” may be of greater practical application, but as yet the data are insufficient from which to draw definite conclusions.

B. Vasoconstrictors. The thought then occurred to some that since it is not practical to bring about a delayed absorption of insulin by physical means such as an oil suspension, that it might be done by decreasing the blood supply of the area into which insulin was to be injected. It has been known from the time of the discovery of insulin that this hormone and pituitrin were antagonistic. That is, if insulin and pituitrin were given at the same time, the insulin did not exhibit its blood sugar lowering effect. This reaction Wermer and Monguio⁸⁴ think is due to the vasoconstriction produced by the pituitrin, and because of this fact, insulin can enter the circulation very slowly. Claussen^{44b} was able to slow down the absorption of insulin by adding to it small quantities of adrenalin or pituitrin. There were no unpleasant reactions from the vasoconstricting drugs used. Anderson,⁶ employing Claussen's technique, treated 17 cases of diabetes. The procedure was to add 0.1 mg. of adrenalin to 5 cc. of insulin and use the necessary dosage as each patient's condition demanded. It was observed that this mixture did not produce symptoms of hypoglycemia, whereas a like quantity of insulin alone did. The decrease in the blood sugar lowering rate was attributed to the slower absorption of the insulin containing the vasoconstrictor.

C. The Salts of Heavy Metals. In 1934, Maxwell⁵⁴ observed that the addition of zinc salts to hypophyseal gonadotropic extracts increased their potency. He stated that the action of zinc consisted in retarding the absorption of the active principle. It has also been shown that zinc prolonged the activity of insulin.^{68a} Furthermore, Maxwell and Bischoff⁵⁵ found that not only zinc, but other metals possess a similar action. They added basic ferric chloride to insulin and found that its absorption from the parenteral depots slowed down. Fazekas and Himwich²³ were able to demonstrate this prolonged action with salts of aluminum. Cobalt and nickel have also been used to delay the absorption of insulin. It is, therefore, apparent that when the salts of a variety of heavy metals are added to insulin, a change occurs which prolongs the activity of insulin, without affecting its pharmacologic properties.

D. Tannic Acid and Safranin O. Maxwell and Bischoff⁵⁵ found that the addition of tannic acid to insulin would also result in a slow acting product. A compound made of 4 mg. of tannic acid and 5 cc. of insulin was shown by Gray²⁸ to act more slowly than the unmodified insulin. However, the insulin-tannic acid compound caused local reactions such as painful swelling and redness.

Another slow acting insulin preparation was introduced by Jacobs and Ricketts.³³ They mixed equal parts of a 0.5% aqueous solution of safranin O and insulin of the U 40 concentration. They then adjusted the pH to the weakly alkaline side (7.2) and obtained a precipitate

which, when injected into animals, caused a hypoglycemia of gradual onset and extended duration.

E. Histone-Insulin. This preparation was proposed by Gray, Bisehoff and Sansum.²⁹ They combined histone, a simple protein, with aqueous insulin. Disodium phosphate was then added and the pH adjusted to 6.7, at which point a finely divided precipitate was formed. The histone-insulin thus formed was used in the treatment of 30 diabetic patients. They reported that it was capable of controlling human diabetes when used alone, that its action was slower than aqueous insulin and that no local or systemic reactions were observed.

It may be of interest at this point to inquire why the addition of heavy metals, histone, tannic acid, or safranin O to insulin results in a compound whose action is of longer duration. The explanation for this phenomenon is lacking. It has been assumed that in the case of the heavy metals this prolonged activity could be explained on the basis of catalysis. This hypothesis cannot be applicable to the tannic acid or the safranin O compound. It seems to us that the following hypothesis might be suggested. As the salts of heavy metals and tannic acid are protein precipitants, it is not at all unlikely that proteins in the subcutaneous areas are precipitated by them, when such metals or tannic acid are injected subcutaneously. As the coagulum or perhaps many coagula are formed, insulin is bound up within them. In time these particles are acted upon by the tissue juices and the insulin gradually liberated, thus prolonging its action.

Sahyun⁶⁵ prepared a crystalline insulin which is completely soluble at pH 6.4 to 7.0. When a solution of this preparation was made it was found that its action was considerably prolonged. Barach⁹ used crystalline insulin in the treatment of 21 cases of diabetes mellitus and concluded that this preparation lowered the blood sugar to a greater extent and for a longer time. He also observed that insulin reactions occurred less frequently than when commercial insulin was used. With the exception of some minor differences of opinion, all investigators^{25,52,61} who have had experience with crystalline insulin agree that its action is prolonged. Altschuler and Leiser⁵ stated that the pharmacologic effect of crystalline insulin may last as long as 14 hours, and because of this prolonged action permit better control of the diabetic patient. Most of the investigators suggested that the prolongation of its activity was due to its zinc content. There may be a qualitative relationship, but certainly no such quantitative factor could be demonstrated. Barach⁹ felt that the greater alkalinity of this product when in solution was the factor responsible for its slower action. He stated that "The greater the alkalinity the slower the absorption of insulin." From the published evidence it is obvious that crystalline insulin acts more slowly than regular insulin, but the explanation for this phenomenon will have to await future developments.

Protamine Insulin. Most of the above methods of slowing up the activity of insulin were interesting but not practical. They could not be used in the treatment of diabetic patients. To Hagedorn,³⁰ however, credit is due for the discovery of a substance which retards the activity of insulin and which at the same time is of tremendous practical value. The substance used was protamine—a simple protein. This was mixed with insulin, and the resulting product was called protamine insulin.

When this product became available it was supplied in two vials—protamine in one and insulin in another. The protamine was so buffered that when the two were mixed the pH changed from 3.5 to 7.2, that is, to the alkaline side. The mixture had a milky appearance due to the suspension of fine flocculent particles. On standing, protamine insulinate would separate into two layers—a white flaky one and a clear, colorless, supernatant fluid. Before using, it had to be shaken gently to make the distribution of the particles uniform, and, like insulin, it had to be used parenterally. Krarup,^{44a} after using this preparation for 2½ years, reported no deleterious results. No undesirable local or systemic reactions were noted by him in the treatment of 41 diabetic patients. He demonstrated in a convincing fashion that protamine insulinate lowers the blood sugar more slowly than insulin and that its action is prolonged. Here, then, was a preparation which was free from deleterious effects, local or systemic, which had practical possibilities, which lowered the blood sugar slowly, thus eliminating sharp sudden hypoglycemic states, and which because of these properties suggested a very desirable improvement in diabetic therapy, namely: the diminution in the number of daily injections.

When this product was first announced, certain pharmaceutical firms placed the material at the disposal of a large and representative group of physicians. Protamine insulinate, or protamine insulin, as it was being called, was thus subjected to much clinical trial. In a short period of time a voluminous literature accumulated and most of the workers commented very favorably. Clinicians^{1,14,26,32,40,47a,48,69,62,63,70,73,78} agreed that the new insulin acted more slowly and that its action was prolonged. The reason for this property is that it is relatively insoluble in the subcutaneous tissues and is therefore more slowly absorbed than the aqueous acid regular insulin. The protamine and the aqueous insulin when mixed produce a physico-chemical reaction in which adsorption plays a dominant rôle. Each flocculent particle adsorbs a certain amount of insulin as if it were a small particle of charcoal. When these congregate particles are administered parenterally, they are acted upon by the tissue juices, and as they are broken down the insulin is liberated and absorbed. The action of protamine insulin, therefore, should be directly proportional to the time required by the tissue juices to liquefy the precipitate. This, however, is unpredictable on theoretical grounds and certainly clinically one can only approximate the duration of the active phase of the product. Its duration of action has been given as from 12 to 24 hours. Regular insulin on the other hand is absorbed rapidly and its pharmacologic effect lasts from 4 to 6 hours.

It is now well recognized that the moderately severe and severe diabetic patient has a rising blood sugar during the night even if no food is taken. Hagedorn³⁰ and his associates felt that protamine insulin given to these patients would counteract the nocturnal blood sugar elevation, and he has also found it possible to obtain a normal fasting morning blood sugar by giving an adequate amount of the new insulin in the evening. His technique was to give soluble insulin in the morning to reduce the elevation of the blood sugar which resulted from the digested carbohydrate, and the insoluble insulin in the evening to maintain the blood sugar at approximate normal levels. This was a most logical beginning, and it was based on sound physiologic principles.

It is not unreasonable to assume that the production of insulin in the organism is subject to variations depending on requirements. This is a cardinal principle in physiology. If one is quiet, the metabolic processes are at a lower ebb than if one is very active. Less gastric juice is secreted during fasting than during a good meal. And so with the production of insulin, a carbohydrate-rich meal is provocative of greater quantities of insulin than a meal of fat or fasting. It is also probably true that the secretion of insulin goes on continuously; otherwise, even in the normal individual the blood sugar would be subject to great variations at night. It is on such a hypothesis that Hagedorn formulated his technique for the use of protamine insulin. The method, while not decreasing the number of injections in all cases, maintained the blood sugar curve throughout the 24-hour period at a level approximating normality.

At this point many clinicians began to use protamine insulin, and modifications of the original technique have resulted from their collective experience. However, no standard technique is as yet available. Most investigators felt that advantage of the prolonged action should be taken and thereby attempt the control of the diabetes by means of a single large dose. Wilder⁶⁵ stated that the action of a single dose might extend into the third day and that its immediate effect was slight. He administered protamine insulin in a single large dose in the morning, at times with, and at times without, regular insulin. He noted that when protamine insulin was used alone in a large single dose, a postprandial glycosuria occurred at first; but that the "end of the fourth to the sixth day a normal level of blood sugar may be obtained even in severe cases." Sprague and his associates⁷⁸ also treated diabetic patients with one injection of protamine insulin, giving the entire daily dose before breakfast. This procedure was followed by others and, though usually satisfactory, in severe cases had to be supplemented by regular insulin to prevent the postprandial glycosuria. Lawrence and Archer⁴⁷ found a single dose of protamine insulin satisfactory with mild cases, but in the severe cases large single doses of 60 to 100 units would not prevent a glycosuria. Campbell, Fletcher and Kerr,¹⁷ on the other hand, found that a single dose of 50 to 60 units of protamine insulin will bring about "fair" control in most severe cases requiring 60 to 100 units of insulin, given in 3 or 4 injections. These investigators were careful to state, however, that in some cases 2 injections of protamine insulin may be more effective in controlling a glycosuria. Joslin's^{39a} counsel in connection with the use of protamine insulin is very sound. He stated that one must be patient, as good results may not show "for several days, a week or longer." He also advised that one change very slowly from the regular to the protamine insulin, allowing a week for the transfer. It was his policy, at first, to hospitalize the patients who wished to transfer from the old to the new insulin.

As the results of the treatment of diabetes with protamine insulin began to appear, all agreed in one respect, that the blood sugar was lowered gradually and that the action of the product was prolonged. Most were of the opinion that the diabetes improved considerably. The use of fewer injections gave patients more freedom, which was of psychologic value. The patient claimed that he definitely felt better. All of this was true, but it was equally true that it was practically impossible in some cases of diabetes to maintain a urine free from sugar.

Some of our patients receiving protamine insulin gained weight, felt well and were free from symptoms, but a marked glycosuria was present throughout the greater part of the day. An analysis of these divergent opinions revealed that two important variables were at work: 1, diet and, 2, technical differences in the administration of the protamine insulin.

Diet. Hagedorn used high-fat diets with about 100 gm. carbohydrates. Campbell, Fletcher and Kerr^{17a} used also diets high in fat and low in carbohydrate. Joslin's diets were more generous in their carbohydrate content. Rabinowitch, Fowler and Corcoran,⁶¹ on the other hand, employed the high carbohydrate-low calorie diet. They were able to control their cases with a single daily dose of protamine insulin. Using similar diets we were not very successful in maintaining our patients free from sugar on one dose of protamine insulin alone. Campbell and his associates^{17b} felt that more satisfactory regulation of the diabetes with protamine insulin could be affected with diets *low in carbohydrate*, and furthermore that it was more feasible to maintain the urines of such patients free from sugar by one daily injection.

Technique. As diabetic patients vary, it is obvious that almost individual methods had to be evolved for each patient. As a result the following combinations of protamine insulin with or without regular insulin have been used.

a, Regular insulin in the morning, protamine insulin in the evening; *b*, protamine insulin in the morning, regular insulin in the evening; *c*, protamine insulin and regular insulin in the morning—these were to be given in separate syringes and into different sites; *d*, large, single, daily doses of protamine insulin in the morning; *e*, protamine insulin and regular insulin in the morning *and* in the evening.

From the data published it appeared that protamine insulin had great possibilities. Of the disadvantages mentioned the chief ones were that: *a*, the protamine and insulin had to be mixed aseptically by the physician or patient; *b*, that the mixture was not very stable and at first it was even recommended that it be discarded after a week's time; and, *c*, that the reactions due to overdosage were somewhat different from those of regular insulin. Fortunately, the question of stability of the mixture required little attention as at this time a supposedly more stable compound was introduced. It is to be stated, however, that Rabinowitch⁶¹ and his associates demonstrated that protamine insulin may show no deterioration after 135 days. Lawrence^{47a} also felt that it was more stable than generally believed.

Protamine Zinc Insulin. Scott and Fisher^{68b} showed that the addition of small quantities of zinc to protamine insulin produced a *more stable and longer acting compound*. Furthermore, the addition of the zinc obviated the necessity of two separate vials for mixing. It could be supplied already mixed. The mixture has a milky appearance, it is stable, it is obtainable in two concentrations, 40 and 80 units per cc., and it contains 0.2 mg. zinc per 100 units. Protamine zinc insulin has replaced the older preparation of protamine insulin.

From the data of the experiences recorded in connection with the use of protamine zinc insulin, clinically and experimentally, the following conclusion may be drawn:

1. It retains its potency for several months after mixing.
2. During the first 3 to 6 hours it shows little if any effect on the blood sugar.
3. Its slow action is due entirely to the slow rate of absorption from the parenteral depots.
4. It lowers the blood sugar slowly.
5. Its pharmacologic effect continues for at least 24 hours when used in moderate doses, and longer with larger ones.
6. That in cases of moderately severe and severe diabetes it must be supplemented with the soluble or regular insulin to eliminate the post-prandial hyperglycemia and glycosuria, particularly if a liberal carbohydrate diet is used.

The technique for its application is still varied. Some clinicians select a definite unitage as a starting point, and after 2 or 3 days alter the dose, being guided by the glycosuria and the blood sugar level. Lawrence and Archer^{47b} begin with a basal dose of 30 units. They then examine two specimens of urine—one immediately on awakening; the other before breakfast. The first specimen represents the urine voided soon after bedtime; the second the urine secreted before breakfast, this being the more informative one. If the second specimen is sugar-free it is an indication that the dose of protamine zinc insulin has been sufficient—providing there are no symptoms of overdosage. If the second specimen contains sugar then the quantity of the preparation must be increased. This simple and most informative procedure will suffice in the mild or even moderately severe cases. In the severe type of case regular insulin will have to be added to take care of the immediate carbohydrate load. Lawrence and Archer^{47b} state that both the protamine zinc insulin and soluble insulin can be mixed in one syringe and injected into one site. They claim that such mixing does not interfere with the individual properties of each preparation.

Another method of arriving at the required dosage is to give about 75 % of the total daily dose of insulin as protamine zinc insulin, supplementing it with regular insulin and adjusting the amount up or down according to the urine and blood tests. Whatever method is employed it is obvious that each patient is an individual problem and must be carefully studied before satisfactory adjustment can be made. Joslin^{39b} is of the opinion that protamine zinc insulin is an advance in the therapy of diabetes and from his experience with 1250 cases he is extremely enthusiastic over the results.

Reactions. The subject of the frequency and type of reactions resulting from the use of protamine zinc insulin has not been sufficiently discussed.

From the first experiences it was the belief that the reactions were mild and infrequent. Then gradually warnings regarding the subtleness of the reactions began to appear, Allen^{2b} being among the first to observe this. Wilder⁶⁵ stated that he heard of 1 death resulting from protamine zinc insulin, and he believes that the reactions have been "unduly minimized." Lawrence and Archer^{47b} also mention the hazard of reactions because of the lack of prodromes, such as sweats, trembling and shakiness. Jordan³⁷ found unconsciousness in 6 out of 17 cases from protamine zinc insulin. While he attributes some of this to carelessness in carrying out the advised treatment, yet hypoglycemic reactions were

also troublesome in the patients who followed instructions and were receiving only 1 daily injection of protamine insulin alone. Tolstoi⁸¹ has reported his experiences with reactions. Severe reactions occurred in 5 out of 15 patients. All patients were experienced diabetics and were fully familiar with the premonitory symptoms of hypoglycemia. Yet, some were not aware that anything was wrong until they became unconscious and had to be revived by means of intravenous glucose or adrenalin. In 4 of the cases reactions took place 24 hours after the injection even though the patients were receiving liberal carbohydrate diet. In no instance were the doses over 45 units at one time. The explanation for the subtleness of reaction and its suddenness is probably that the blood sugar is lowered so gradually that tremor, sweats, shakiness and palpitation are absent. Tolstoi has also stated that the reactions due to protamine insulin may strike suddenly, without warning, and once established may last a long time.

Summary. The above review has presented the extradiabetic uses of insulin, of which there are many. The application of this hormone in some pathologic conditions has been based on physiologic principles; in others on purely empiric grounds. Even though miraculous results have been reported, it is difficult to ascribe the therapeutic benefits to insulin alone. One cannot deny, however, that insulin stimulates the appetite and can be of value in disease or health when it is desirable to increase the body weight. Insulin, as a cure for schizophrenia, has had considerable publicity and hundreds of cures can be found in the literature. In spite of the enthusiastic reports, experienced psychiatrists, while keenly interested advise great caution and patience.

We have also presented the arguments for the need of a slow acting insulin and described most of the preparations used. An attempt has been made to explain the *modus operandi* of each. It will be seen that to date the most practical slow acting insulin is protamine insulin to which zinc has been added. The technique employed in connection with its clinical application have been described and the symptoms as well as the hazards resulting from overdosage have been presented.

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BIBLIOGRAPHY.

- (1.) Adlersberg, D.: Wien. klin. Wchnschr., 49, 476, 1936. (2.) Allen, F. M.: (a) Am. Rev. Tuberc., 34, 230, 1936; (b) J. Am. Med. Assn., 107, 430, 1936. (3.) Allen, F. M., Douglas, S. A., Warren, E. L., and Pottenger, W. E.: Am. Rev. Tuberc., 34, 257, 1936. (4.) Altschul, A.: J. Am. Med. Assn., 106, 1380, 1936. (5.) Altshuler, S. S., and Leiser, R.: Ibid., 107, 1626, 1936. (6.) Anderson, T. T.: Acta med. Scand., 86, 361, 1935. (7.) Baker, H.: Rev. Gastroenterol., 3, 258, 1936. (8.) Banyai, A. L., and Jurgens, G. H.: Am. J. Med. Sci., 188, 76, 1934. (9.) Barach, H. H.: Ann. Int. Med., 10, 9, 1937. (10.) Beale, S. M.: Am. J. Surg., 17, 413, 1932. (11.) Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, Baltimore, William Wood & Co., p. 931, 1937. (12.) Block, J.: Wien. Arch. f. inn. Med., 23, 257, 1932. (13.) Blotner, H.: (a) Med. Clin. North America, 15, 991, 1932; (b) J. Am. Med. Assn., 100, 88, 1933; (c) New England J. Med., 211, 103, 1934. (14.) Bowcock, H.: South. Med. J., 29, 701, 1936. (15.) Bowen, B. D., and Lockie, L. M.: J. Lab. and Clin. Med., 21, 505, 1936. (16.) Buresch, A.: Klin. Wchnschr., 11, 1420, 1932. (17.) Campbell, W. R., Fletcher, A. A., and Kerr, R. B.: (a) Am. J. Med. Sci., 192, 589, 1936; (b) Trans. Assn. Am. Phys., 51, 161, 1936. (18.) Cheng, Y. L., and Lyman, R. S.: J. Nerv. and Ment. Dis., 83, 281, 1936. (19.) Copeman, W. S. C.: Brit. Med. J., 2, 1130, 1931. (20.) Current Comment: J. Am. Med. Assn., 108, 560, 1937. (21.) Danzer, C. S.: Med. Rec., 142, 180, 1935. (22.) Dimitracoff, C.:

- Progrès. méd., 1, 421, 1932. (23.) Fazekas, J. F., and Himwich, H. E.: J. Pharm. and Exp. Ther., 58, 260, 1936. (24.) Feuillade, H.: Lyon méd., 151, 469, 1933. (25.) Freund, H. A., and Adler, S.: J. Am. Med. Assn., 107, 573, 1936. (26.) Geyelin, R. W.: Personal communication. (27.) Glueck, B.: (a) J. Am. Med. Assn., 107, 1029, 1936; (b) New York State J. Med., 36, 1473, 1936; (c) J. Nerv. and Ment. Dis., 85, 564, 1937. (28.) Gray, P. A.: Endocrinology, 20, 461, 1937. (29.) Gray, P. A., Bischoff, F., and Sansum, W. D.: Ann. Int. Med., 11, 274, 1937. (30.) Hagedorn, H. C., Jensen, B. N., Krarup, N. B., and Wodstrup, I.: J. Am. Med. Assn., 106, 177, 1936. (31.) Himwich, H. E., and Nahum, L. H.: Am. J. Med. Sci., 133, 608, 1932. (32.) Jacobi, H.: New York State J. Med., 37, 349, 1937. (33.) Jacobs, H. R., and Ricketts, H. T.: Proc. Soc. Exp. Biol. and Med., 35, 473, 1936. (34.) Jankelson, I. R., and Norman, J.: Trans. Am. Gastro-Enterol. Assn., 36, 322, 1933. (35.) John, H. J.: (a) Endocrinology, 17, 583, 1933; (b) Ibid., 19, 689, 1935. (36.) Jones, C. R.: Am. J. Digest. Dis. and Nutr., 1, 135, 1934. (37.) Jordan, W. R.: Virginia Med. Month., 63, 730, 1937. (38.) Jorge, A. L., and Sobrinho, J. P.: Presse méd., 40, 1951, 1932. (39.) Joslin, E. P.: (a) New England J. Med., 215, 1166, 1936; (b) J. Am. Med. Assn., 109, 497, 1937. (40.) Joslin, E. P., Root, H. F., Marble, A., White, P., Joslin, A. O., and Lunch, G. W.: New England J. Med., 214, 1079, 1936. (41.) Katsch, G., Scholderer, H., and Klatt, K.: Ztschr. f. klin. Med., 129, 608, 1936. (42.) Klaffen, E.: Wien. klin. Wchnschr., 48, 1509, 1935. (43.) Kohne, G. J.: Am. J. Digest. Dis. and Nutr., 2, 447, 1936. (44.) Krarup, N. B.: (a) Clinical Investigations into the Action of Protamine Insulinate, Copenhagen, G. E. C. Gad, 1935; (b) Ibid., quoted by.
- (45.) Lambret, O., and Driessens, J.: Bull. Assn. franç. p. l'étude du cancer, 25, 77, 1936. (46.) Lasch, F.: Med. Klin., 28, 1675, 1932. (47.) Lawrence, R. D., and Archer, N.: (a) Brit. Med. J., 1, 747, 1936; (b) Ibid., 1, 487, 1937. (48.) Levitt, A., and Castiglia, C. F.: Am. J. Digest. Dis. and Nutr., 4, 413, 1937. (49.) Leyton, O.: Lancet, 1, 756, 1929. (50.) Liegner, B.: Zentralbl. f. Gynäk., 59, 2883, 1935. (51.) McCabe, J., and Hart, J. F.: New York State J. Med., 33, 924, 1933. (52.) Mains, M. P., and McMullen, C. J.: J. Am. Med. Assn., 107, 959, 1936. (53.) Mauriac, P., Broustet, P., and DuBarry: Bull. Acad. de méd. (Paris), 108, 1445, 1932. (54.) Maxwell, L. C.: Am. J. Physiol., 110, 458, 1934. (55.) Maxwell, L. C., and Bischoff, F.: Ibid., 112, 172, 1935. (56.) Metz, R. D.: Ann. Int. Med., 6, 743, 1932. (57.) Modern, F. S.: Med. J. and Rec., 136, 163, 1932. (58.) Monat, H. A.: Med. Bull. Vet. Admin., 12, 403, 1936. (59.) Mosenthal, H. O.: Personal communication. (60.) Nichol, E. S.: Am. J. Digest. Dis. and Nutr., 2, 236, 1935. (61.) Rabinowitch, I. M., Foster, J. S., Fowler, A. F., and Corcoran, A. C.: Canad. Med. Assn. J., 35, 239, 1936. (62.) Ralli, E. P.: Personal communication. (63.) Root, H. F., White, P., Marble, A., and Stotz, E. H.: J. Am. Med. Assn., 106, 180, 1936. (64.) Rosenberg, H., and Kereszturi, C.: Quart. Bull. Sea View Hosp., 1, 76, 1935. (65.) Sahyun: Quoted by Wilder, R. M., and Wilbur, D. L.: Arch. Int. Med., 59, 329, 1937. (66.) Sakel, M.: (a) Zeit. Neur., 143, 506, 1933; (b) Wien. klin. Wchnschr., 46, 1372, 1933; (c) J. Nerv. and Ment. Dis., 85, 561, 1937. (67.) Schlesinger, B., and Keele, K. D.: Arch. Dis. Child., 10, 149, 1935. (68.) Scott, D. A., and Fisher, A. M.: (a) J. Pharm. and Exp. Therap., 55, 206, 1935; (b) Ibid., 58, 79, 1936. (69.) Sezary, A., and Friedman, E.: Bull. Soc. franç. de derm. et syph., 42, 1426, 1935. (70.) Sherrill, J. W., and Copp, E. F.: Publication of Scripps Metabolic Clinic, San Diego, Calif., La Jolla, June, 1937. (71.) Sinelnikov, S. N., Perchik, P. M., and Doroklova, O. N.: Klin. Med., 13, 1474, 1935 (Abstr. J. Am. Med. Assn., 106, 259, 1936). (72.) Skouge, E., and Shrumph, A.: Ztschr. f. klin. Med., 120, 754, 1932. (73.) Smith, B.: Calif. and West. Med., 45, 144, 1936. (74.) Smith, H. M.: J. Am. Med. Assn., 108, 1959, 1937. (75.) Smith, K. S.: Brit. Med. J., 1, 693, 1933. (76.) Spellberg, M. A., and Rosenblum, S. H.: Am. Rev. Tuberc., 34, 376, 1936. (77.) Sperber, P.: Rev. Gastroenterol., 3, 320, 1936. (78.) Sprague, R. G., Blum, B. B., Osterberg, A. E., Keppler, E. J., and Wilder, R. M.: J. Am. Med. Assn., 106, 1701, 1936. (79.) Strecker, H.: München. med. Wchnschr., 83, 649, 1936. (80.) Throne, B., and Myers, C. N.: Urol. and Cutan. Rev., 40, 322, 1936. (81.) Tolstoi, E.: New York State J. Med., 37, 1279, 1937. (82.) Walker, J. E., and Wiley, W. D.: J. Am. Med. Assn., 105, 196, 1935. (83.) Wegierko, J.: (a) Presse méd., 44, 729, 1936; (b) Wien. klin. Wchnschr., 50, 163, 1937. (84.) Wermer, P., and Monguio, J.: Klin. Wchnschr., 1, 748, 1933. (85.) Williams, G. A., and Williams, R. L.: J. Am. Med. Assn., 104, 1208, 1935. (86.) Wilson, R.: J. So. Carolina Med. Assn., 32, 83, 1936. (87.) Wortis, J.: (a) J. Am. Med. Assn., 108, 971, 1937; (b) J. Nerv. and Ment. Dis., 85, 581, 1937; (c) Ibid., p. 565; (d) Quoted by.

RADIOLOGY

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LOW BACK PAIN.

Low back pain associated with so-called sciatic radiation has been recognized for centuries as a clinical entity. The obvious localization of pain in the low back frequently associated with a deformity of the spine early led to the conclusion that the radiation of pain in the leg was produced by some lesion in the low back. Various explanations, such as myositis, joint infection, lumbosacral abnormalities or derangement of the sacroiliac joints, have each in their time held sway as the plausible etiologic factor for this symptom-complex of sciatic irritation associated with low back pain. Interest has been stimulated by the possibilities of mechanical nerve irritation demonstrated anatomically by Danforth and Wilson,⁷ and substantiated clinically by Putti,²³ Ayers¹ and later Williams.²⁵ With this introduction Badgley² presented the clinical features of low back pain with sciatic radiation observed in a study of 447 cases as a prelude to the roentgenographic study reported by Hodges and Peck.¹¹ The clinical picture of this group was characterized by the onset, sudden or gradual, in an hitherto normal individual, of low back pain associated with a radiation of pain into the lower extremity along an almost constant pathway in the posterolateral part of the extremity, the buttock, the anterolateral and posterolateral part of the thigh and the anterolateral part of the leg and foot. The cases were subdivided into three groups, all with low back pain and radiation into the lower extremity, but differing in the extent of radiation or deformity: 1, Typical sciatic scoliosis characterized by the symptoms of low back pain with radiation usually along the described pathway in the lower extremity plus the development of a list of the trunk away from, or toward the affected side, rarely the list alternating to one or the other side. 2, Symptoms of low back pain, with radiation the full extent of the lower extremity without the list, or a history of the list. 3, Low back pain with radiation of pain into one or both buttocks, associated with pain deep in the thigh. No pathological process that precluded the possibility of spontaneous return to normal function was included in this study, thus ruling out all cases of tuberculosis, tumors, osteomyelitis, and so forth.

The more characteristic symptoms were briefly: 1, Pain, seeming to center about the posterior sacroiliac region into the buttock, deep in the thigh in the posterolateral portion, following the peroneal division of the sciatic nerve. This pain was generally constant, aggravated by motion or change of position. The radiation pain was also usually constant, but occasionally intermittent and brief in nature, brought on

by sudden unguarded movement. No case presented radiation of pain along the tibial nerve distribution and only a small number had radiation of pain on the mesial side of the thigh. 2, Guarded motion of the spine was early assumed by the patient. Spinal motion was prevented as much as possible by unusual use of the arms in changing positions such as getting up from a chair, or turning over in bed. 3, A list of the trunk was present in 173 cases (39%), away from the affected leg in 125 and toward the painful side in 81. In 233 cases (61%) the list was not present but there was a protective attitude on standing with the weight borne on the well leg, and the painful leg held in flexion and abduction bearing little weight. Commonly, the most comfortable attitude assumed by this group was to stand bent over the back of a chair or table with the weight borne on the hands, the affected leg flexed and abducted.

Clinical tests of definite value in the diagnosis were: 1, Straight leg raising was usually limited, generally more limited on the painful side, frequently producing pain in the low back in the lumbosacral or sacroiliac region. This was probably due to the contraction of the lumbopelvic muscles, altering the tilt of the pelvis and producing an apparent shortening of the hamstring muscles. 2, Patrick's sign, forced abduction of the flexed thigh producing pain in the sacroiliac region, was not commonly present. Compression of the iliac crests rarely elicited pain. Where these tests were positive they tended to incriminate the sacroiliac joint as the seat of the lesion. 3, Nachlas' sign, hyperextension of the thigh with the patient prone and the knee flexed, frequently produced pain in the lumbosacral region and was a test of the lumbosacral joint. 4, The prone thrust test, the patient lying prone, raising himself on his hands with elbows extended, and dropping the pelvis toward the table as far as possible, was used frequently. This produced hyperextension of the spine and in itself was frequently painful or impossible to carry out because of pain in the lumbosacral region. If not painful in itself, with the patient relaxed in this attitude, a sudden thrust over the lower lumbar spine sharply increased hyperextension and frequently produced severe pain analogous to the patient's symptoms. 5, Ober's sign, an attempt to adduct the extended abducted leg with the knee at right angles, the patient lying on the side, was infrequently used. The test was positive if the knee could not be brought to the table but remained in an abducted position and this was indicative of contraction of the iliotibial band. In cases with positive tests a high division of the iliotibial band (Ober's operation) has resulted in marked relief of symptoms. 6, Sensory changes were present in only 20% of cases, mild hyperesthesia or hypesthesia over the peroneal distribution. 7, The sites of tenderness in the 447 cases were tabulated as lumbar spine (63), lumbosacral (260), posterior iliac spines (212), lumbosacral articular facets (33), sciatic notch (195), deep nerve (66) and no point of tenderness (53). 8, Motor changes were exceedingly rare; there was muscular weakness probably due to disuse noted in 12 cases and a true paralysis in only 2 cases in the entire series. 9, The Achilles reflex was definitely altered in 80 cases (18%), usually diminution and less frequently complete absence. 10, Atrophy of $\frac{1}{2}$ inch or more of

the affected leg was frequently noted, this feature was practically constant in the severe chronic cases, undoubtedly on a disuse basis.

Males constituted 56.7% in this series. The average age, varying from 13 to 80 years, was 49.7 years. A few cases with prolonged symptoms of years' duration added somewhat to the average duration of symptoms of 4.24 years. Occupation seemed to play a definite part in the etiology; 168 were housewives, 91 unskilled laborers, and 84 skilled laborers. Trauma was regarded as a definite cause in only 25% of cases; 86 patients had sudden onset of symptoms immediately after trauma and 29 had a gradual onset which they attributed to a preceding injury. Without a history of trauma, 42 patients had sudden onset and 288 had a gradual onset of symptoms. There was but a single attack in 15 cases, recurrent attacks occurred with intervals of complete freedom in 230 cases, symptoms were constant in 108 cases and in 92 cases there were constant symptoms plus acute exacerbations associated with radiation of pain to the leg. The symptoms were recorded as mild in 183 cases, there was temporary incapacitation by the severity of the symptoms in 165 cases. Eighty-four patients were incapacitated from their usual occupation and 15 were completely incapacitated by the severity of the symptoms.

There was a characteristic pathway for radiation of pain arising from the region of the posterior spines of the ilium, over the buttock and trochanter, down the posterolateral and anterolateral surface of the thigh, the anterolateral surface of the leg and foot. The distribution of pain was not the distribution of the sciatic nerve. The area of involvement is the so-called dorsal axial surface of the leg which is supplied by the postaxial nerves of the anterior divisions which compose the lumbosacral plexus, and could be more properly called postaxial plexalgia.

Lumbosacral tenderness is not an uncommon finding in patients with just a low back pain, whereas the tenderness about the sacroiliac region was seen chiefly in this syndrome. Tenderness over the sciatic exit was also a frequent finding in this series.

The symptomatology was characteristically the same whether the roentgenogram showed a normal spine, congenital malformation, narrowing of the lumbosacral joint space, arthritis, or asymmetrical development. The type of skeletal change observed in the roentgenogram had no definite relation to the extent and location of the radiation of pain. It seemed plausible that a true neuritis was more apt to occur in the presence of definite lumbosacral lesions. The sensory changes also occurred with greater frequency in the abnormal Roentgen group than in the normal.

Hodges and Peck¹¹ made a routine Roentgen study of the dorsal, lumbar and sacral spine in all the cases clinically considered by Badgley and for purposes of comparison reviewed comparable spine films of a control group of cases. The findings of the two groups were tabulated. Narrow lumbosacral joint was noted in patients with low back pain and sciatic radiation in an approximate ratio of 4.5 to 1 found in patients with low back pain and no sciatic radiation. Lumbosacral anomalies were seen in approximately 2 patients with low back pain

and sciatic radiation to 1 with low back pain and no sciatic radiation. There was no significant difference in the study group and in the *control group* as regards osteoarthritic changes. The distribution of the different types of lumbosacral anomaly observed in the group of patients with low back pain and sciatic radiation was tabulated.

In his Hunterian lectures, Keith¹³ described the human spine as a mechanism of the utmost complexity. Between the sacrum and the skull are incorporated 24 vertebræ, each provided with 3 short levers—the transverse processes and the spinous process. Each lever is furnished with not a single muscle, but a group of them. Passing from the sacrum to the skull one finds the levers change in length, strength, shape and direction. The muscles too which move and balance the levers alter in disposition and strength from vertebra to vertebra. The 12 dorsal vertebræ, besides their 3 short processes, are provided with very long and powerful levers—the ribs. They are the most powerful of the spinal levers. All the muscles attached to the ribs—the intercostals, the rectus abdominis, and the oblique muscles of the belly wall—are prime movers and balancers of the spine.

With the evolution of the upright or orthograde spine there took place a shortening of the lumbar part of the spinal column. The 3 vertebræ which became modified in the course of development to form the sacrum were the twenty-seventh, the twenty-eighth and the twenty-ninth. The twenty-seventh formed the first of the sacral series in the earliest mammals. In some monkeys the twenty-seventh showed some admixture of lumbar traits. In others, the twenty-sixth showed signs of forsaking some of its lumbar traits and adapting the characters of the first sacral. There was a tendency in some for the process of sacralization to spread in a tailward direction, in others the tendency was in a headward direction. In a majority of chimpanzees the twenty-fifth became the first sacral, but among the orangs the twenty-fourth (fifth lumbar) formed the first of the sacral series. In man, as in the chimpanzee and gorilla, the twenty-fifth formed the first of the sacral series. In a series of 100 human skeletons approximately 3 or 4 show a headward sacralization, while 6 or 8 show a tailward movement. In a similar number the eighteenth vertebra will bear the last rib in about 2, the nineteenth in 90 and the twentieth in 8.

The brunt of the evolutionary or adaptional changes fell on the spinal musculature of the lumbar region. The spinal musculature obtained an ever-increasing attachment to the sacrum and pelvis. The pelvis became more and more a fixed base from which the erector spinæ might act. In man the area for muscular origin was also increased by the backward tilting of the sacrum, so that its dorsal surface in the erect position looked upward as well as backward. The spine, transmitting the weight of the suprapelvic part of the body became poised on the anterior or basal end of the sacrum. The weight tended to tilt up the hinder or coccygeal end of the sacrum and would have done so were it not for, 1, the form and strength of the sacroiliac joints and, 2, because the hinder end of the sacrum was bound to the ischial tuberosities by those particularly strong stays, the sacroiliac ligaments. There was also a tendency, when the sacrum was set obliquely, for the basal end of the spine to be dislocated forward into the pelvis, giving

rise to the condition known as spondylolisthesis. Such a dislocation was prevented by the articular processes of the last lumbar vertebra being locked within those of the sacrum. A sudden jump, or a severe effort to lift or carry a heavy weight, might cause the laminar arch of the last lumbar vertebra to snap and thus permit a forward displacement of the spine. Keith found no evidence which would lead him to suppose that the separation of the arch of the last lumbar vertebra was the result of maldevelopment.

Kark¹² considered faulty posture to be the underlying cause of much genital change in women. The lumbar vertebræ are held in position mainly by the anterior and posterior common ligaments, the supraspinous and interspinous ligaments. These are kept taut or relaxed according to the attitude of the spine and are subject to strain. When this strain is constantly repeated or prolonged, aching results. The ligaments are reinforced by the sacrospinalis muscle, which extends from the sacrum to the cervical region. This muscle is a large muscular and tendinous mass, larger in the lumbar region than elsewhere, and it is by its aid that spinal movements take place and the trunk is held erect, the brunt of such action falling on the lumbosacral region. When this muscle is strained, therefore, or when it is not strong enough to carry out its normal or increased functions, aching results in the lumbosacral region. The frequent association of backache with such conditions as retroversion, subinvolution, dysmenorrhea, congestion of the pelvic organs, is probably due to the existence of a common etiological factor, namely, a weak back, loss of muscle tone and faulty posture. This might serve to explain why the treatment of retroversion and other gynecological disorders seldom relieves backache unless the back itself is treated, even to the neglect of a local displacement. The lumbar arch is in many respects analogous to the plantar arch in the foot. In the condition of flat foot, aching is caused by strain on the ligamentous structures of the flattened and weakened arch. This ache can usually be relieved by mechanically supporting the sagging arch. Further, by means of suitable exercises and massage, the muscles that normally support the arch are gradually strengthened until such time as the mechanical support can be dispensed with and the arch maintained by muscles and ligaments that have been rested and restored to function.

Goldthwait *et al.*,¹⁰ in discussing the relation of body mechanics to disease, pointed out that the weight of the trunk and head rests mostly on the bodies of the vertebræ and the intervertebral discs. The articular facets normally act only as stabilizers. The articular processes of the adjoining lumbar vertebræ, with their facets, form the posterior wall of the intervertebral foramina. Where these two articular processes come together, there is a true joint with a capsule and ligaments. This joint has a normal range of motion. The amount of motion will vary with the shape of the facets. In the lordotic position of the lumbar spine the weight of the body is thrown backward upon the articular facets. Strain from faulty mechanics, therefore, must come on the articular facets and the joint capsule instead of on the body of the vertebræ. If this strain is great enough to cause inflammatory reaction and swelling of these ligaments and joints, the possibility of

narrowing the intervertebral foramina is very real. The spinous processes in lordosis may impinge on one another, and in extreme lordotic curves may act as a fulcrum and cause a stretching strain on the joints of the articular processes. If this backward strain was severe enough, these joints might be subluxed or even dislocated. Transverse processes may impinge on the wings of the sacrum, forming a true joint, or they may become firmly fused or sacralized. These changes will limit the possible amount of motion at this region of the spine in all directions and if, as one grows older, the curves of the spine become habitually increased, make more possible strains or irritations in this region.

Brown³ summarized this phase in his statement that the fundamental principles were: 1, A joint which is used habitually in a position which has free motion in either direction has a small potential of injury. Such a joint has the so-called factor of safety motion. 2, A joint which has a small or no factor of safety motion has a definite potential of injury. 3, The best treatment for an injured joint is: first to correct the weight-bearing lines in order to regain the factor of safety motion, and then to be sure that function is carried out in good weight-bearing lines.

Danforth and Wilson⁷ found that in only a small proportion of patients with sciatica could an etiologic factor of a general or constitutional nature, such as diabetes, syphilis, alcoholism, lead poisoning, and so forth, producing an inflammatory or degenerative change directly in the nerve be elicited. Likewise, vertebral tuberculosis and neoplasms, intrapelvic or extrapelvic tumors or inflammations producing pain either by direct pressure upon, or irritation of, the sciatic nerve at some point in its course or at its roots were comparatively rare. Essential or idiopathic sciatica (sciatic scoliosis) presented a clinical picture sufficiently striking to have earned for it a description as a disease entity. Goldthwait⁹ was the first to investigate the problem from the anatomic and mechanical standpoint. He first called attention to the frequent occurrence of vertebral abnormalities, such as sacralization of the transverse process of the fifth lumbar vertebra and asymmetrical development of the posterior articulations, and pointed out the etiologic rôle which they, in combination with faulty body posture, might play in the production of sciatic pain. By their investigation, which included a series of dissections, they proved that the intervertebral foramen between the fourth and fifth lumbar vertebrae was always the smallest; that the fifth lumbar nerve root was usually the largest; the fifth nerve root was directly anterior to the posterior articulation between the fifth lumbar vertebra and the sacrum, and effusion in this joint might easily cause compression. Manipulation of the anatomic specimens demonstrated that hyperextension of the spine caused the posterior superior articular facets of the posterior joints to be driven upward toward the inferior intervertebral notches of the vertebra next above and in this way diminished the size of the intervertebral foramen exerting pressure on the nerve. Narrowing of the intervertebral disc between the fifth lumbar and first sacral vertebrae had the same effect.

Putti²³ considered sciatica as a symptom from the clinical standpoint.

In a diagram he illustrated the differentiation into neuritis, plexitis, funiculitis, ganglionitis and radiculitis, according to the area of the nerve-root involvement. In roentgenographic studies one is concerned only with funiculitis, because here only is pain found associated with anatomic alterations. The fourth and fifth nerves are those possessing the longest funicular portion of all those which constitute the lumbar plexus, that is they have the longest course through the intervertebral foramina. The funicular portion of the nerve does not lie within the arachnoid, but is only clothed by dura mater, and it is not bathed in cerebrospinal fluid. Around the funiculus there is a very rich venous plexus, which is much influenced by mechanical conditions outside the funiculus. This absence of arachnoid and a protective layer of fluid exposes the nerve to these outside mechanical influences and the surrounding venous plexus puts it at the mercy of any congestion or stasis that may occur in the neighborhood from any one of numerous causes. Variations in the direction of the articular facets in the joint between the fifth lumbar and first sacral vertebrae not infrequently alter the shape and reduce the capacity of the intervertebral foramina and these articulations may be the site of a localized arthritis, which itself may irritate the nerve trunk.

Mixter and Ayer¹⁹ reported 34 cases of herniation or rupture of the intervertebral disc into the spinal canal. Pain was the first symptom in every case and it was for relief of pain that all except 2 sought relief; in the 2 cases disability was of prime importance. The pain was usually described as an ache in the low back, usually just to one side or the other, becoming paroxysmal on turning, stooping, coughing or sneezing, whereupon it would radiate outward over the buttock and down the back of the thigh, and at times the back of the leg also. Not infrequently the pain commenced in the midline and radiated down the back of both thighs, but unilateral distribution was the rule, even though symptoms had lasted many months. Pain in the perineum was also present in 3 patients. In only 1 was the pain referred to the anterior aspect of the thigh. In spite of great pain, little objectively determined sensory loss was the rule, and only rarely was bilateral saddle anesthesia obtained. This condition was first described in 1911 independently by Goldthwait in America and Middleton and Teacher in England; but these contributions seem to have been forgotten. In the meantime, reports of enchondroma or ecchondroma of the intervertebral disc began to appear and this interpretation continued in spite of the statement of their pathologist that the tumor on section looked like normal intervertebral disc. Mauric,¹⁷ in 1933, from a study of the literature came to the conclusion that many of the so-called enchondromata and Schmorl's nodules (herniations of the nucleus pulposus) were identical. About the same time their clinical observations brought the same conclusion. The condition was rare compared with back strain, fracture, sacroiliac strain and the like. Examination of the spinal fluid and Roentgen ray examination with lipiodol were of the greatest importance in diagnosis.

Spondylolisthesis is another condition in which intractable low back pain brings the patient for examination. The first clinical observations were reported in the latter part of the Eighteenth Century. Kilian¹⁵ (1853) gave it the name spondylolisthesis, a combination of the Greek words meaning slipping of the vertebra. Neugebauer²⁰ (1892) aroused interest in the subject, chiefly among obstetricians. There has been a considerable discussion as to the part of congenital separation of the neural arch, unilateral or bilateral, occurring through the laminae between the superior and inferior facets, and trauma, in the occurrence of this lesion. Congdon,⁶ in a study of a series of spines, found this anomaly in 5% of these and quoted Willis²⁶ as having elicited 4.8% in a similar study. From his observations Congdon felt that only a considerable separation would be discernible in the roentgenogram of the living subject. Other writers have asserted that all the results of anatomic and clinical study oblige one in most cases to look on injury as the cause. Primary fracture of the interarticular portion of the neural arch of the fifth lumbar was probably the most frequent. Congenital anomalies are at least a predisposing factor in many cases. Roentgenographically, an ovoid shadow appearing over the upper sacral segment in the anteroposterior projection is suggestive, a roentgenogram made in the lateral projection will reveal a subluxation of one vertebral body on the adjoining one, usually the fifth lumbar on the first sacral, a lengthening of the diameter from the tip of the spinous process to the anterior border of the affected vertebra over that of the contiguous one, and a "hump" in the outline of the neural canal at the point of involvement. A vertical line at right angles to the lower border of the vertebra above will pass anterior to the body of the dislocated vertebra in spondylolisthesis and through the body in the normal. Fixation by bone graft may be necessary for the relief of symptoms.

From the extensive literature covering the various phases of this interesting symptom some essays have been selected for this review that have not been specifically acknowledged, but these have been included in the bibliography to afford a more comprehensive study to those particularly interested in the subject as a whole.

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BIBLIOGRAPHY.

- (1.) Ayers, C. E.: *New England J. Med.*, 196, 9, 1927; 200, 592, 1929. (2.) Badgley, C. E.: *Am. J. Roentgenol.*, 37, 454, 1937. (3.) Brown, L. T.: *J. Bone and Joint Surg.*, 30, 157, 1932. (4.) Capener, N.: *Brit. J. Surg.*, 19, 374, 1932. (5.) Chandler, F. A.: *Surg., Gynec. and Obst.*, 53, 273, 1931. (6.) Congdon, R. T.: *J. Bone and Joint Surg.*, 30, 511, 1932. (7.) Danforth, M. S., and Wilson, P. D.: *Ibid.*, 7, 109, 1925. (8.) Ghormley, R. K.: (a) *Minnesota Med.*, 14, 249, 1931; (b) *J. Am. Med. Assn.*, 101, 1773, 1935. (9.) Goldthwait, J. E.: *Boston Med. and Surg. J.*, 164, 365, 1911. (10.) Goldthwait, J. E., Brown, L. T., Swaim, L. T., and Kuhns, J. G.: *Body Mechanics in the Study and Treatment of Disease*, Philadelphia, J. B. Lippincott Company, 1934. (11.) Hodges, F. J., and Peck, W. S.: *Am. J. Roentgenol.*, 37, 461, 1937. (12.) Kark, C. L.: *Brit. Med. J.*, 1, 348, 1931. (13.)

Keith, A.: *Ibid.*, 1, 499, 1923. (14.) Key, J. A.: *AM. J. MED. SCI.*, 168, 526, 1924. (15.) Kilian, H. F.: Quoted by Chandler.⁵ (16.) Kimberley, A. G.: *Western J. Surg., Gynec. and Obst.*, 43, 699, 1935. (17.) Mauric, G.: *Medecine*, 14, 705, 1933. (18.) Meyerding, H. W.: (a) *J. Bone and Joint Surg.*, 29, 39, 1931; (b) *Surg., Gynec. and Obst.*, 54, 371, 1932. (19.) Mixter, W. J., and Ayer, J. B.: *New England J. Med.*, 213, 385, 1935. (20.) Neugebauer, F. L.: Quoted by Chandler.⁵ (21.) Ober, F.: *J. Bone and Joint Surg.*, 18, 105, 1936. (22.) Pitkin, H., and Pheasant, H.: *Ibid.*, 18, p. 111. (23.) Putti, V.: *Lancet*, 2, 53, 1927. (24.) Sashin, D.: *Ann. Surg.*, 32, 932, 1936. (25.) Williams, P. C.: *J. Am. Med. Assn.*, 99, 1677, 1932. (26.) Willis, T. A.: *J. Bone and Joint Surg.*, 29, 709, 1931.

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CENTENARY OF GERHARD'S DIFFERENTIATION OF TYPHOID FROM TYPHUS FEVER.

"Thus, the triple lesion of the glands of Peyer, mesenteric glands and spleen, constituting the anatomical characteristic of the dothinenteritis of typhoid fever, although sought for with the greatest care, evidently did not exist in the epidemic typhus."
(AM. J. MED. SCI., 19, 302, 1837.)

AMONG the many noteworthy articles that have appeared in this JOURNAL during the 127 years of its existence none is of greater importance than W. W. Gerhard's contribution "On the Typhus Fever, which occurred at Philadelphia in the Spring and Summer of 1836; illustrated by Clinical Observations at the Philadelphia Hospital; showing the distinction between this form of disease and Dothinenteritis or the Typhoid Fever with alteration of the follicle of the small intestine." As this notable landmark in early American medical literature appeared in this JOURNAL in 1837 (February and August numbers), it is appropriate to commemorate its centenary at this time.

For the younger medical generation of today to whom typhoid fever has become almost a medical rarity, it must be difficult to visualize what an important step in medical progress this paper represents. Not only did this admirable clinico-pathologic study—in the best Louis tradition—segregate once and for all an important single disease, but it is perhaps of even greater significance from its effects in making a definite break in the hitherto confused mass of the continued fevers. This is not the place to go into any details of this complex situation that had lasted for centuries; nor is such action necessary, as the story has been well told elsewhere, especially by Dr. William H. Welch in the first Gerhard lecture of the Philadelphia Pathological Society (Proc., 28, 42, 1925). We wish at this time merely humbly to commemorate the centenary of one of this JOURNAL's most important articles.

THE EDITORS.



WILLIAM WOOD GERHARD (1809-1872)

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DECEMBER, 1937

ORIGINAL ARTICLES.

A CLINICAL LECTURE AS OF TWENTY-FIVE YEARS AGO.

By HENRY A. CHRISTIAN, M.D.,

PHYSICIAN IN CHIEF, THE PETER BENT BRIGHAM HOSPITAL; HERSEY PROFESSOR OF
THE THEORY AND PRACTICE OF PHYSIC, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

(Given in the Amphitheatre of the Peter Bent Brigham Hospital, May 27, 1937,
on the Occasion of the 25th Anniversary of the Class of 1912 of the
Harvard Medical School.)

It so happens that the twenty-fifth anniversary of the graduation of the Class of 1912 from the Harvard Medical School is a particular anniversary in my own medical life. In September, 1908, you of the Class of 1912 were beginning your medical careers. In that same year I was beginning the teaching of Medicine from the Chair of the Theory and Practice of Physic. This Chair at Harvard University has a past history indicating its great comfort. It is an historical fact that the Professors of the Theory and Practice of Physic all have looked on medical life from that chair for long periods of time. Benjamin Waterhouse, its first occupant, began early in life to sit in the chair and continued there for 30 years. Nobody has ever occupied it for less than 15 years, and the majority range between 15 and 30 years. If my activity continues through to my academic demise, I shall beat out old Benjamin by one year and establish a record for the chair.

This afternoon I am going to ask you to take yourselves back to the autumn of 1910 and place yourselves once again on the benches in the lecture room in the Medical School and let us re-discuss much as we did then a topic illustrated by a patient who was not present at the exercise, because in that year my patients were in South Boston at the Carney Hospital, and my amphitheatre for teaching was just across the street from here in the Harvard Medical School buildings.

We started in the early autumn of 1910 on a discussion of nephritis and I think it may be of interest today to pass around to you the classification of nephritis that we were then using.

CLASSIFICATION OF NEPHRITIS.

Lecture No. 1.

Pathological classification.

Clinical classification.

1. Acute degenerative nephritis
2. Acute exudative glomerulonephritis
3. Acute proliferative glomerulonephritis
 - a. Capsular glomerulonephritis
 - b. Intracapillary glomerulonephritis
4. Acute non-suppurative interstitial nephritis
5. Acute suppurative interstitial nephritis

Acute nephritis

6. Subacute glomerulonephritis
7. Chronic parenchymatous nephritis
Amyloid nephritis
8. Chronic interstitial nephritis
Arteriosclerotic

Subacute nephritis

Chronic parenchymatous

Chronic interstitial

I began my lecture by running over the classification of nephritis that had been given to you in the Department of Pathology and pointed out that a pathologic classification was not practical for application to every day clinical cases. Having myself taught in pathology and conducted the laboratory work for 3 years, I let you in on a little secret, namely, that the specimens of kidney, the sections of which you studied in your course in pathology, were accumulated with great difficulty from an enormous amount of material. Pathologists had worked hard to obtain those specimens for you, because ordinarily autopsies show a multiplicity of lesions in any single nephritic kidney. If one tries to apply to clinical work a pathologic classification such as the one you were taught, one becomes considerably confused. To avoid this, a large group (5) of the acute forms of nephritis in the pathologic classification were brought down clinically to just one, acute nephritis.

There were two forms of chronic nephritis in the pathologic classification; you will note the nomenclature of 25 years ago, interstitial and parenchymatous nephritis. In between the extremes of acute and chronic nephritis is a group, which was put down as subacute. This probably is closer in pathologic resemblances to the acute than the chronic. Clinically for these we used the same terms as in the pathologic classification, we spoke of subacute nephritis, chronic parenchymatous nephritis and chronic interstitial nephritis. Today, it is more fashionable to speak of chronic glomerular and chronic vascular or arteriosclerotic nephritis.

Now let us turn to our case of 25 years ago.

He was a boy aged 15, with an essentially negative past history, except for an interesting sequence of childhood diseases. He had had mumps, measles and whooping cough all before he was 6 years of age. From 6 to 15

he had had no acute infectious disease of any sort. He first came into the hospital on September 21, 1908.

About 6 months before entry he had a septic condition in his knee. It was described as purulent arthritis. Judging, however, by the scar of the drainage incision and the perfection of the function of his knee joint, it is likely that he had merely an infection about rather than in his joint. He was well until September 15, that is, 6 days before he came into the hospital, when he had a severe attack of colicky pain in the abdomen. The pain persisted in a succession of attacks, which lasted anywhere from a few minutes to an hour or two, and were most severe in the right lower quadrant, though radiating to a certain extent over the entire abdomen. The bowels were loose rather than constipated. He knew of no recent dietary indiscretion.

He entered on the surgical service. His physical examination essentially was negative except for a slight degree of tenderness in his right lower quadrant brought about by pressure over it. The next morning his appendix was removed, and it was normal except for two small concretions. He stayed in the hospital from September 21 to October 1 and was sent home well.

On October 4, 3 days after he went home, while sitting up in a chair, he was seized with severe abdominal pain in the region of the liver, aching in quality, which lasted for half an hour. His bowels were constipated; he vomited a liquid, greenish material with pain. He was very sure that he had eaten nothing indigestible.

The symptoms continued until his second entrance to the hospital, on October 11. The pain, however, began to decrease so that he felt very much better on the day of entry than he felt previously; he even was strong enough to walk about the ward without any discomfort before he was put to bed. But the next morning he vomited again and had recurrence of pain now so intense that it caused him to draw his legs up over his abdomen.

He had been passing the usual normal amount of urine during his illness. He had lost a little weight.

He was rather undernourished and pale. His tongue was a bit coated. His radial arteries seemed, for his age, very definitely thickened. The lungs and heart seemed quite normal. There was slight edema of both ankles. Over both buttocks, and over the internal and external surfaces of the lower legs and feet there was a macular eruption, the macules being dark red to brownish in color and about the size of a pin head.

His urine showed albumin; the first specimen contained 0.25%, the second specimen 0.7%, the third specimen 0.6%. The specific gravity of the specimens were 1.009, 1.020, 1.023. The amount of urine excreted was somewhat decreased. Each specimen contained numerous finely and coarsely granular and epithelial casts, a few leukocytes and a few red cells. These represented the usual findings in his urine during his stay in the hospital.

The rash gradually decreased, disappeared, reappeared on October 22 and subsequently disappeared. On October 21 it was noticed that he had a little swelling of his face. The boy thought we were not giving him enough to eat, and his mother thought we were starving him, so she took him home. He left the hospital on October 22.

On November 12 he reappeared at the hospital now giving this story. Since leaving us he had stayed in bed part of the time, at first feeling fairly well. But presently his legs and scrotum began to swell. He had no headache, no return of the rash, no abdominal pain, no vomiting, no chills.

His urine now was a little scantier than it had been, a little more concentrated than previously, contained a little more albumin, but in the sediment had essentially the same cast picture.

The physical examination was very different. He had a coated tongue. The heart was perhaps a trifle enlarged on percussion. Over both backs, below the angle of the scapula, there was dulness on percussion, decreased breath sounds and distant, fine, crackling râles. His belly was distended, tympanitic in the upper part with dulness in the flanks. There was marked edema, beginning at his toes and going up over his abdomen with excessive edema over his scrotum. His weight, having been stated when he was well to be 108 pounds, was now 122 pounds; in a few days it increased to 123 $\frac{3}{4}$ pounds and then began to decrease as the fluid began to recede. By Thanksgiving time, November 26, he was fairly free from edema. He celebrated Thanksgiving well if not wisely. He made special arrangements on his own responsibility with the cook, and she behind the screen served him a regular Thanksgiving dinner, which he ate.

The evening of November 27 he had a little headache. The next day he did not want any food, and the idea of Thanksgiving dinner was very repugnant. At 2 A.M. that night he suddenly jumped out of bed, ran to the bathroom, was caught by the nurse and carried back to bed. He would not tell why he went to the bathroom. He slept the rest of the night from 2 A.M. on. At 7 A.M. he was found struggling in bed, with pupils dilated and twitching of the eyes, his eyes opening and shutting rapidly; he was thrashing his head from one side to another and at times not breathing, during which period he became cyanosed.

The condition was relieved by pulling the jaw forward as his throat became filled with mucus. He breathed freely. Between 7 A.M. and 9 A.M. he had 8 such convulsive seizures. He then remained quiet until about 2 P.M., when he had another convulsion. This quieted down, and he had no more until 8 P.M., when he had another and 3 the following morning. Subsequently he had no more.

During the period when he had his seizures, he became semicomatose, but gradually improved, cleared up mentally and 50 hours after the attacks started he was just about in the condition he was before they began. Nothing else particularly happened.

We kept him in the hospital until February 19. The edema by then had all disappeared, he was gaining weight and was feeling very well. The urine was not very different from what it was when he first came in, but it seemed wise to let him go home. His eye grounds showed nothing abnormal and I read in some of my lecture notes that I demonstrated to you 25 years ago an electric ophthalmoscope, showing how easy it was to use and how definitely it should be a part of the armamentarium of every doctor.

The middle of that following summer (June, 1909) he noticed that his urine was very dark in color and decreased in amount. This frightened him so that he came back into the hospital. He now weighed 118 pounds, looked well and had no edema. His urine contained a little albumin plus many casts. He stayed in the hospital for a few days and then went home.

He was seen again on October 5, 1910. Now his blood pressure had gone up. Up to this time it had been normal, now it was 150. No other changes were noted. He had now gained in weight to 134 pounds.

I saw him for the last time 2 years after his first admission, that is, in January, 1911. His blood pressure had returned to normal. His weight was 147 $\frac{1}{2}$ pounds. His urine had a very slight trace of albumin and a very rare hyaline cast. He had been working steadily for 2 years in a machine shop running a lathe, and he felt perfectly well.

Now you notice that this history up to the note of October 5, 1910 antedated the time that I presented it to you (October 4 of that year). On that occasion we discussed this case. It may be interest-

ing to re-discuss it much as we did then, contrasting our views of it then with our present views.

One of the features of the case that seemed interesting was the possible effect of the appendectomy in the development of the nephritis. I spoke to you of the effects of ether in patients with or without renal disease and described to you a patient that I had had a few years before when I was inaugurating the clinical clerkship in Medicine at the Massachusetts General Hospital, which, by the way, I had the pleasure of starting with Dr. R. H. Fitz, in the autumn of 1905. With a group of students I observed a patient's specimen which, standing in the old fashioned urine glass that they used at the Massachusetts General Hospital, had a greenish, grayish sediment of about 1 inch at the bottom of the urine glass, which consisted almost entirely of granular casts. There was only the very slightest possible trace of albumin in this urine. The patient had received a considerable amount of ether the day before the urine was passed. The next day the urine was clear; there was not a trace of albumin and only an occasional hyaline cast. The next day the urine was entirely normal. I tried to leave you with the idea that an anesthetic might irritate the kidneys, but by and large one need not worry much about anesthesia as far as the kidney was concerned, unless there was some very serious preëxisting renal disturbance. This view I still maintain.

Another point that seemed of interest 25 years ago was the possibility of estimating by clinical observation the type of pathologic changes in the boy's kidney according to the classification of nephritis which we then were using. I pinned one of the members of the class down to offering the opinion that the boy's kidney was large and that the nephritis, essentially, was of the glomerular type. On the other hand, it seemed impossible clinically to predict minute microscopic changes as for instance whether the patient had, as Dr. Councilman used to say "an intracapillary proliferative glomerular lesion" or some other type of lesion. It was suggested that in all probability there also were degenerative changes in the epithelial cells, and that if one looked, one might find fat in the urine.

The skin lesions provoked much interest. Finally the class evolved a very interesting and modern point of view regarding their probable significance. We concluded that in the light of what was known, nephritis was not solely a disease of the kidney but also was a general systemic disease which involved the entire capillary system. Blood cells appeared in the urine due to weakening of the renal capillaries, and in similar fashion, edema appeared in the skin, weakened skin capillaries might give way and so cause the skin lesions such as were observed.

Together we analyzed carefully the history. We discussed the patient's abdominal pain, which apparently was not related to any abdominal pathologic process in the sense of appendix or gall-bladder

disease, and pointed out that abdominal pain is not a very uncommon symptom in acute nephritis and sometimes may also occur in the early stages of chronic nephritis; also we reminded ourselves that abdominal pain is not an unusual symptom in patients who have purpuric spots and that possibly this patient had a form of Hensch's purpura to explain his attacks. We knew that this patient had edema, that the edema cleared up and was followed by a uremic stage of 2 or 3 days' duration when convulsive seizures with coma appeared; that then he came out of this and gradually got better, his urine improved, and the albuminuria grew less. But a short time later, after a stage of apparent improvement, one day he noticed that his urine had become very dark and bloody again, and that the process had exacerbated, again to clear up until eventually the patient was working every day at a job and was seemingly healthy.

All this discussion naturally led to the matter of prognosis. In my opinion, it depended on whether this patient was developing a granular kidney or not. If so, the prognosis would probably be expressed by saying that the case would gradually change into the picture of chronic interstitial nephritis and the patient would probably live 4 or 5 years with it. Yet, on the other hand, it was perfectly possible for him to continue to excrete albumin and a certain number of casts and have very little change from now on in his renal condition. He even might stay clinically well almost indefinitely, because part of his kidney tissue would recover and become normal kidney and carry on the function of the kidney, although certain foci would remain injured, and these would furnish albumin and casts, while the good tissue would keep the machinery going effectively. On the other hand, I warned you to remember that subsequent acute illnesses would be likely to cause exacerbations. I believed it probable that this particular boy would develop chronic interstitial nephritis and go down hill fairly quickly; but I knew of people who had excreted albumin and casts and only after 20 or 30 years of this died of uremia.

Next we took up the mechanism of edema, and it is quite interesting, I think, to run over this subject, as told to you 25 years ago, and contrast it with the explanation which our present fourth year men give when they are asked what is the pathologic physiology of edema.

- We emphasized the fact that the glomerulus in its diseased condition must interfere with the excretion of fluid and thereby theoretically should lead to what was spoken of as hydremic plethora. Against this theory was the fact that, as a rule, it was very difficult to demonstrate any increase of fluid in the blood, or hydremic plethora, in a patient with nephritis, and when "hydremic plethora" was demonstrable, it usually, though not always, failed to correspond with the edema. The patient who was not edematous might show plethora, and the patient who had edema might not show it.

Then we considered the relationship of edema to salt retention, and I cited to you cases in which the intake of salt seemed to control the accumulation or the disappearance of the edema fluid; but pointed out that that was not the whole answer, because there was a very definite group of cases that had marked salt retention and never had any edema at all. In the old fashioned terminology, such cases were those with chronic interstitial nephritis. I made a practical suggestion that in the management of an edematous patient, it was wise to try a restriction of salt, and if this method of dieting worked to lessen the edema, to continue with it; but that if it did not work, not to keep on with a saltless, unpalatable diet known to be accomplishing no good.

Another theory regarding the mechanism of edema was that the important cause lay in a generalized vascular lesion, a diseased condition of the small blood-vessels all over the body. In explanation of edema of such origin we could not offer very much from the clinical side, but we could offer a good deal from the experimental pathologic side. As I pointed out, in 1888, in Chittenden's laboratory in New Haven, Dr. Samuel Lambert, subsequently Professor of Medicine at Columbia University Medical School, Dean at the College of Physicians and Surgeons and Chief Physician at St. Luke's, and who by the way still is living, began to use uranium nitrate and found that this produced in rabbits nephritis of a form with which was associated edema, whereas other experimental substances would produce acute nephritis but without edema. Then I reminded you that in 1875 or 1877, about the time Dr. William Welch was working in Cohnheim's Laboratory, Cohnheim had shown that one could give animals things that produced kidney lesions, but such animals did not develop edema, even if a large amount of fluid was administered. But if one irritated the skins of such animals by rubbing on chloroform, the irritated part of the skin would become edematous. This observation suggested that some local skin condition on top of a background of renal disease made for edema. Finally, about 1908, Dr. Richard M. Pearce had been working in Philadelphia at the University of Pennsylvania on the problems of edema, stimulated somewhat by the well known interest of the late Dr. Weir Mitchell in snake bite. Dr. Pearce knew that if a rattle-snake bit an individual in the arm, let us say, the individual's arm swelled up and there developed an enormous amount of edema and hemorrhage in the tissues near the site of the wound. He found that if one injured the kidney of an animal with something like potassium bichromate that would not produce edema, and to the same animal gave snake venom short of producing hemorrhage, the vascular system was injured and edema developed.

From such observations, therefore, it seemed reasonable to believe that perhaps the most important part of the mechanism of edema was related to injury of the peripheral vascular system by toxic substances formed or not excreted in nephritis. That is exactly the

explanation that would be given today for the edema of the early stages of acute nephritis.

It is very interesting, that although in regard to salt retention we went into the idea of osmotic pressure of fluid and used the salt retention osmosis relationship to explain the edema in some patients, we had nothing to say about the plasma proteins, which now seem important in the mechanism of edema. My lectures were given to you in the autumn of 1910. In 1896 Starling had described the relationship of osmotic pressure of proteins to fluid exchange between blood-vessels and tissue spaces, pointing out that as the albumin content of the plasma was decreased, osmotic pressure changed, and the fluid exuded out of the vessels faster than it was taken up by the veins. Clinicians apparently paid no attention to Starling's work and made no use of it until much later. I certainly did not, notwithstanding the fact that Starling came over to this country 3 or 4 years before my lectures to you and gave a lecture on that particular subject.

It took 10 or 12 years more before physicians realized the importance of this physiologic idea, for it was not until 1920 or thereabouts that they began to talk of it. Leo Loeb in a very extensive review of the causes of edema published in 1923-1924 mentioned Starling's ideas, but did not think them especially important. Today in order to explain the formation of edema, we talk about capillary permeability, salt retention and now add the effect of variations of the plasma protein as part of the mechanism of edema, realizing that not one single factor, but combinations of varying factors lead to edema.

There is one more topic that we took up at the clinic 25 years ago, namely the frequency of high blood pressure in cases with chronic renal lesions. Dr. Roger I. Lee had very recently published a study calling attention to the relation of high blood pressure to the lesions in the kidney. We discussed his observations and came to the conclusion that the prime factor in hypertension was peripheral vascular constriction in some way related to the lesion in the kidney. This is about all one can say with certainty about high blood pressure in nephritis today, 25 years later.

It has been a great pleasure to me to welcome you back today and repeat for you again a clinical lecture on nephritis. Your faces are somewhat changed, perhaps, but not much more than has changed our physiological conception of chronic nephritis in 25 years. The more I have looked at each of you during this lecture, the more unchanged have each of you seemed to be. I now see smiles again that I used to see frequently. But today on the seats I do not see anybody asleep, while that was not a very uncommon experience 25 years ago. Perhaps this is an omen signifying your greater interest in medicine. I hope that many of you will be here at your fiftieth reunion to consider nephritis, edema and high blood pressure.

VACCINATION AGAINST EPIDEMIC INFLUENZA WITH ACTIVE
VIRUS OF HUMAN INFLUENZA.*

(A TWO-YEAR STUDY.)

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THE studies reported here concern the results of intramuscular vaccination of human beings in large State Colonies with active virus of human influenza, covering the epidemics of respiratory infections of two winters, 1935-1936 and 1936-1937.

Since 1933 when Smith, Andrewes, and Laidlaw¹ first isolated in ferrets the W.S. virus from nasopharyngeal washings of an individual suffering from epidemic influenza, in practically all subsequent sharp outbreaks studied, viruses of closely similar antigenic properties have been isolated. Also during the past winter, 1936-1937, from a pandemic involving European countries, the British Isles, and the United States, closely similar viruses were isolated.

These viruses have not been found in the absence of influenza epidemics and when injected intranasally in ferrets and mice cause a disease which is practically identical with influenza of varying degrees of severity in human beings. When repeatedly injected into these animals by other routes than the respiratory tract, no disease is produced, but on the other hand an immunity to the disease is obtained. Following repeated injections of active influenza virus, it is as yet uncertain how long immunity remains.

The probable etiologic relationship of these viruses to influenza has been shown on human volunteers by Smorodintseff, *et al.*⁵ when the great majority suffered attacks following inhalation of a virus-containing spray.

Magill and Francis³ produced in the serum of the rabbit, a naturally immune animal, for a short period neutralizing antibodies specific only for the strain of virus injected. Later, however, cross

* These studies were assisted by a grant from the Bureau of Animal Industry, United States Department of Agriculture, and by the Lyophile Serum Fund donated by the Board of Managers of the Abington Memorial Hospital.

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neutralizing antibodies appear in the serum with or without an additional intraperitoneal injection of virus. In these experiments the results "would suggest contrary to previously expressed opinion¹ that the swine virus comprises a more complex antigen than the human strains and that the common antigen which elicits the cross neutralizing antibodies is more effectively present in the swine virus."

Despite the demonstrated differences in the antigenic components of the influenza virus strains so far isolated, nevertheless, in a consideration of the production of immunity in the susceptible or in the nonsusceptible animal, it is significant that repeated injections by other routes than the respiratory tract of any one of the human strains isolated has given cross-protection against all of the other strains. For this reason the production of active immunity in human beings against epidemic influenza with one or more of the virus strains has appeared worthy of trial and has resulted in the studies previously reported⁶ and in the present further extension of those studies.

Method of Vaccination. In our earlier studies both the human influenza virus of Francis (PR-8) and the swine influenza virus of Shope (S-15) were used for intramuscular injection. Berkefeld filtrates of suspensions of infected mouse lungs free as far as could be determined from any other organism pathogenic for man, were used as vaccines, whereas during the more recent studies active human virus (PR-8) grown on chick embryo tissue cultures, was used. The reasons for the use of active human virus rather than of inactivated virus for vaccination have been discussed previously.⁶ In 1935-1936, a single colony* of approximately 800 individuals was available for study; in 1936-1937, four additional State Colonies and one private institution were made available, including in all slightly over 5000 individuals. In the winter of 1935-1936, 110 individuals were injected with active human virus (PR-8) and 138 with active swine virus (S-15) in mouse lung emulsion, while the rest of the colony (550) remained unvaccinated. In 1936-1937, all except 8† of those vaccinated during the previous winter season again received active human virus (PR-8) intramuscularly in the form of chick embryo tissue cultures, and in addition approximately one-third of each of the new colonies added to the study were vaccinated with the latter type of vaccine. In contrast to the first season, all vaccinations were performed during the fall and early winter at a time when respiratory infections were minimal.

The chick embryo tissue culture vaccine was grown in large oval culture flasks of 1 liter. A single 13-day chick embryo was finely divided in 200 cc. of Tyrode's solution to which the virus culture was added and the culture was incubated for 48 hours. Of this culture 2 cc. were injected intramus-

* We are indebted to the Department of Institutions and Agencies of the State of New Jersey for their interest and coöperation in these studies.

† On account of the discharge and deaths of a few inmates during the period of study, the numbers in the colonies mentioned throughout are necessarily approximate. Such changes were insufficient to interfere with the statistical analysis of the results, and occurred proportionately among vaccinated and unvaccinated inmates. For instance, in Colony N. L. among those whose vaccinations were completed on December 15, 1936, there were 10 who were not present in the Colony when the epidemic started on January 20, 1937. Slightly more than 275 individuals had been vaccinated so that the groups in Table 3 remained relatively unchanged.

cularly at weekly intervals for 3 doses. The potency of the virus culture was tested in mice before and after injections and a similar fourth dose was injected if any single batch of vaccine failed to show typical lung lesions in mice in a dilution of 1:1000. The method of giving intranasal instillations and of determining lesions in mice has been previously described.⁶

All of the inmates were housed in cottages, the first third alphabetically in each cottage being chosen for vaccination. In two of the colonies in which influenza epidemics later occurred there were also common dining and amusement halls which insured fairly close contact of all the inmates.

Results. Mild local reactions were noted at times when virus-infected mouse lung was used as the vaccine, and in one instance there was a rather severe local reaction. Such reactions were absent when the chick embryo virus vaccine was used, aside from mild soreness such as occurs from a similar injection of 2 cc. of human serum. In a very few individuals and usually within 24 hours following the second injection of the latter vaccine, a slight watery discharge from the nose and "stuffiness" were noted, resembling in some respects a common cold. This cleared rapidly and appeared to be a transient vasomotor response, possibly of an allergic nature. From one such individual, vaccinated in another institution in Philadelphia, nasopharyngeal washings injected intranasally into an anesthetized ferret gave no evidence of the presence of influenza virus. Such reactions* usually followed the second injection of vaccine, were afebrile, evanescent, and without generalized signs or symptoms. Neither among the 1700 vaccinated individuals nor among the 3300 unvaccinated who in each cottage were in quite intimate contact with those vaccinated, was there any evidence of respiratory infection as a result of the vaccination. During the period of vaccination of all colonies from October, 1936, to January 1, 1937, there were no epidemics of respiratory disease, and from the records of all colonies it was noted that during the last months of 1936 there was unusual freedom from respiratory infections. Because of the large number of mice required (approximately 11,000) for study of the neutralizing properties of the sera both before and after vaccination in 1935-1936,⁶ a representative number of sera were obtained at similar intervals during 1936-1937 from all but one of the colonies studied. These neutralization tests will be reported later.

Clinical Results. Epidemics of influenza during 1936-1937 occurred in Philadelphia and in two of the colonies, N.L. and J., as shown by recovery of human influenza virus from nasopharyngeal washings through ferret passage. Probably also the disease occurred a little later in a few cottages of Colony S., although in so

* One of us, P. H. L., Jr., injected chick embryo tissue culture virus intradermally into a number of individuals known to be allergic to chicken, and to egg, without any general reaction.

few individuals that nasopharyngeal washings were not obtained.* Colony S. is so large, about 1450 inmates, that a number of febrile respiratory infections may occur without assuming epidemic proportions. In Colony N.L. a similar epidemic had occurred during the previous season (February and March, 1936).⁶ In this epidemic the human influenza virus was in all probability the causative agent since neutralizing antibodies appeared in the sera of unvaccinated children in the epidemic area around the colony during convalescence when none were present in their sera during the illness. Studies of the nasal and throat washings from the febrile cases in this epidemic were not sufficient to furnish significant data. This epidemic, previously reported, is summarized in this report (Table 1) since it has a bearing on the epidemic in the same colony and in the other colonies, in 1937. In Table 2 are recorded the days of fever in each group. From this table it appears possible that a certain amount of protection was afforded by the S-15 virus vaccine, even though the incidence of febrile respiratory infections in this group and in the unvaccinated group were approximately the same. Excellent protection against the epidemic disease appeared to be afforded by the PR-8 virus vaccine.

TABLE 1.—SUMMARY OF CLINICAL RESULTS—COLONY N.L., MARCH, 1936.

Group.	Number in group.	Febrile.		Afebrile.	
		Cases.	%	Cases.	%
Unvaccinated	550	69	12.5	59	10.7
S-15 vaccinated	138	17	12.4	20	14.3
PR-8 vaccinated	110	3	2.7	16	14.5

Application of the X^2 test to these data shows that the observed differences in the febrile cases between the PR-8 vaccinated and the unvaccinated groups are significant.

TABLE 2.—DAYS OF FEVER: 89 CASES OF UPPER RESPIRATORY INFECTION, COLONY N.L., MARCH, 1936.

Group.	Vaccine.	Total days of fever.	Days fever per person.
A	Human	9	.08
B	Swine	39	.28
C	None	253	.46

Colonies N.L. and J. have had closer and more frequent contact with urban centers than the other four colonies. In their epidemics of 1937 the first cases of respiratory infections were among employees who had been visiting in such centers, and among boys who had been on vacation.† The epidemic of influenza as studied by Francis and Magill² in New York City had reached its height in the latter part of December, and a less severe influenza epidemic reached its

* Although the majority of the febrile respiratory infections were considered to be influenza at the time of occurrence, so few ferrets were then available that it was considered wiser to wait for a spread of the disease throughout the colony before obtaining nasopharyngeal washings. This spread did not occur.

† Vacations are allowed from Colonies N.L. and J., but from none of the other institutions studied.

height in Philadelphia during the early part of January. In Colony N.L. the influenza epidemic began on about January 20, 1937, reaching its height through February, while in Colony J. a smaller epidemic started about February 1, 1937, and reached its height at approximately the same time. The three intramuscular injections at weekly intervals were completed in Colony N.L. on December 15, 1936, whereas they were completed in Colony J. on November 28, 1936. The signs, symptoms and course of the disease were characteristic of what was noted throughout most of the United States during this same period, with certain slight variations in the different colonies studied.

In Chart I is recorded graphically the course of the 1937 epidemic at Colony N.L. It will be noted that before and after the epidemic when only afebrile respiratory infections were occurring, there was little if any difference in incidence of infections between the vaccinated and unvaccinated groups. This equal incidence of afebrile respiratory infections in the vaccinated and unvaccinated groups among all the colonies when free of epidemics is striking evidence favoring the statistical value of differences in incidence of febrile infections between the two groups when the epidemics occurred.

Each peak of febrile infections in the unvaccinated group was closely followed by a peak of afebrile infections in the same group, without any corresponding peaks of infection in the vaccinated group. From this it would appear that afebrile respiratory infections which were actually mild influenza occurred while the incidence of febrile influenza was dropping toward the end of the epidemic, but that this sudden rise of mild influenza did not occur in the vaccinated group due possibly to the protection afforded by the vaccine. It is also interesting that at the height of the epidemic during the week when there were 25 febrile cases in the unvaccinated group, only 2 febrile cases occurred among the vaccinated group. After March 1st, the nature of the respiratory infections in the febrile cases markedly changed. At this time there was no longer the sudden onset with chill, generalized aches, and pains, followed by a racking cough, but rather a purulent type of infection involving the nose and throat practically free of cough in the early stages, but with a thick purulent discharge from the sinuses. It appeared possible that this was entirely of bacterial origin; a hypothesis partially confirmed by the fact that from nasopharyngeal washings taken at this time the human influenza virus could not be isolated.

Previously on February 2 and February 4 from all pools of nasopharyngeal washings taken from unvaccinated individuals, human influenza viruses had been isolated. The washings from one vaccinated individual were included in one of these pools without separation from the other washings, and it is therefore impossible to determine whether or not the human influenza virus was present in his secretions, as distinguished from the secretions of others in

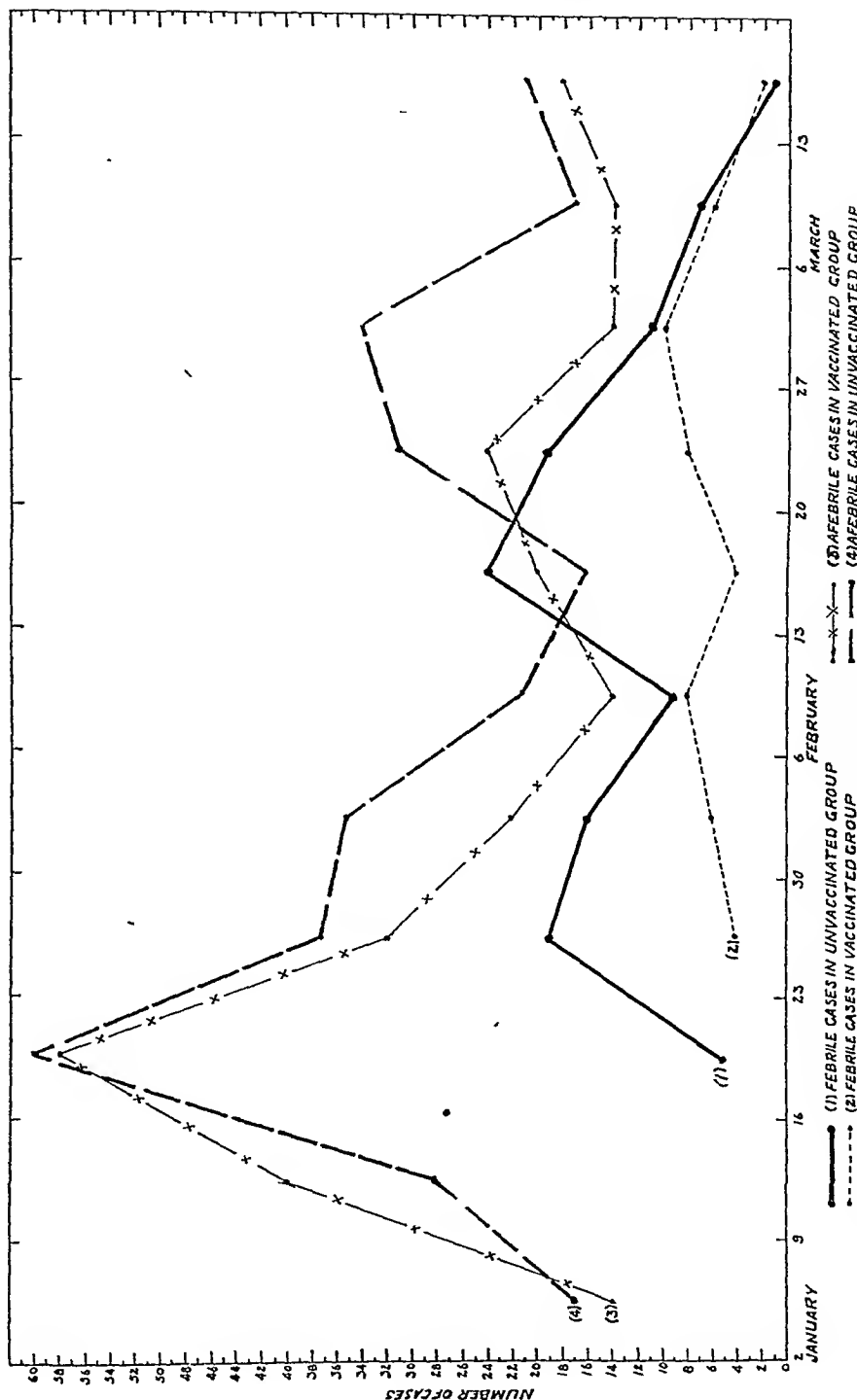


CHART I.—Each point on the graphs represents the total number of cases for each week as shown on the abscissa. For proper comparison the 2 lines for the vaccinated group represent approximately twice the actual incidence of cases, since the unvaccinated group in the colony was approximately twice the size of the vaccinated group.

the same pool. Due to the alteration in the character of the febrile infections and to the inability to obtain human influenza virus during this same period, Table 3 includes all febrile respiratory cases from January 20 to March 1, at which time the incidence of febrile cases was rapidly decreasing. Table 4 gives a comparison of the number of days of fever in the two groups. In this colony the majority of the white blood cell counts during the epidemic were between 3000 and 6000, and while some were as high as 9000, very few fell above this figure. Of those with temperatures of 102° and over there were 36 individuals among the unvaccinated group and only 5 among the vaccinated group; an indication of the marked difference in severity between the groups. The marked difference in total days of fever in the two groups as shown in Table 3 also indicates the difference in severity. The majority of those with high temperatures in the vaccinated group, however, appeared to be typical cases of influenza with characteristic signs, symptoms, and a low white cell count.

TABLE 3.—INCIDENCE OF RESPIRATORY INFECTIONS AT COLONY N.L., JANUARY 20 TO MARCH 1, 1937.

Group.	Number in group.	Febrile.		Afebrile.	
		Cases.	%	Cases.	%
Unvaccinated . .	525	95	18	176	33.5
Vaccinated . . .	275	16	5.8	71	25.8

Application of the χ^2 test to these data shows that the observed differences in the febrile cases between the PR-8 vaccinated and the unvaccinated groups are significant.

TABLE 4.—COMPARISON OF DAYS OF FEVER AND HEIGHT OF FEVER IN TWO GROUPS, COLONY, N.L.

Group.	Total days.	Days per case.	Average per individual.	Cases with 102°-102.8°	Cases with 103° and over.
Unvaccinated	311	3.3	.59	22	14
Vaccinated	37	2.3	.13	2	3

Among the 107 inmates who had been vaccinated in March, 1936, with the human influenza virus (PR-8) and again in December, 1936, there were 4 with febrile respiratory infections occurring during the epidemic. The dates of their admission to the hospital were January 26, January 30, February 10, and February 22, 1937. Among the 133 inmates who had been vaccinated in March, 1936, with the S-15 virus, and again in December, 1936, with the PR-8 virus, there were 6 with febrile respiratory infections occurring during the epidemic. The dates of their admissions to the hospital were January 25, February 2, 18, 22, and 27. Among the 16 febrile cases who had been vaccinated, there were 6 who had received only one course of virus vaccine, *i. e.*, December, 1936.

Chart II graphically represents the smaller epidemic in Colony J. The same rise in incidence of the afebrile cases while the incidence of febrile cases was falling in the unvaccinated group is evident. Table 5 shows a comparison of the incidence of respiratory infec-

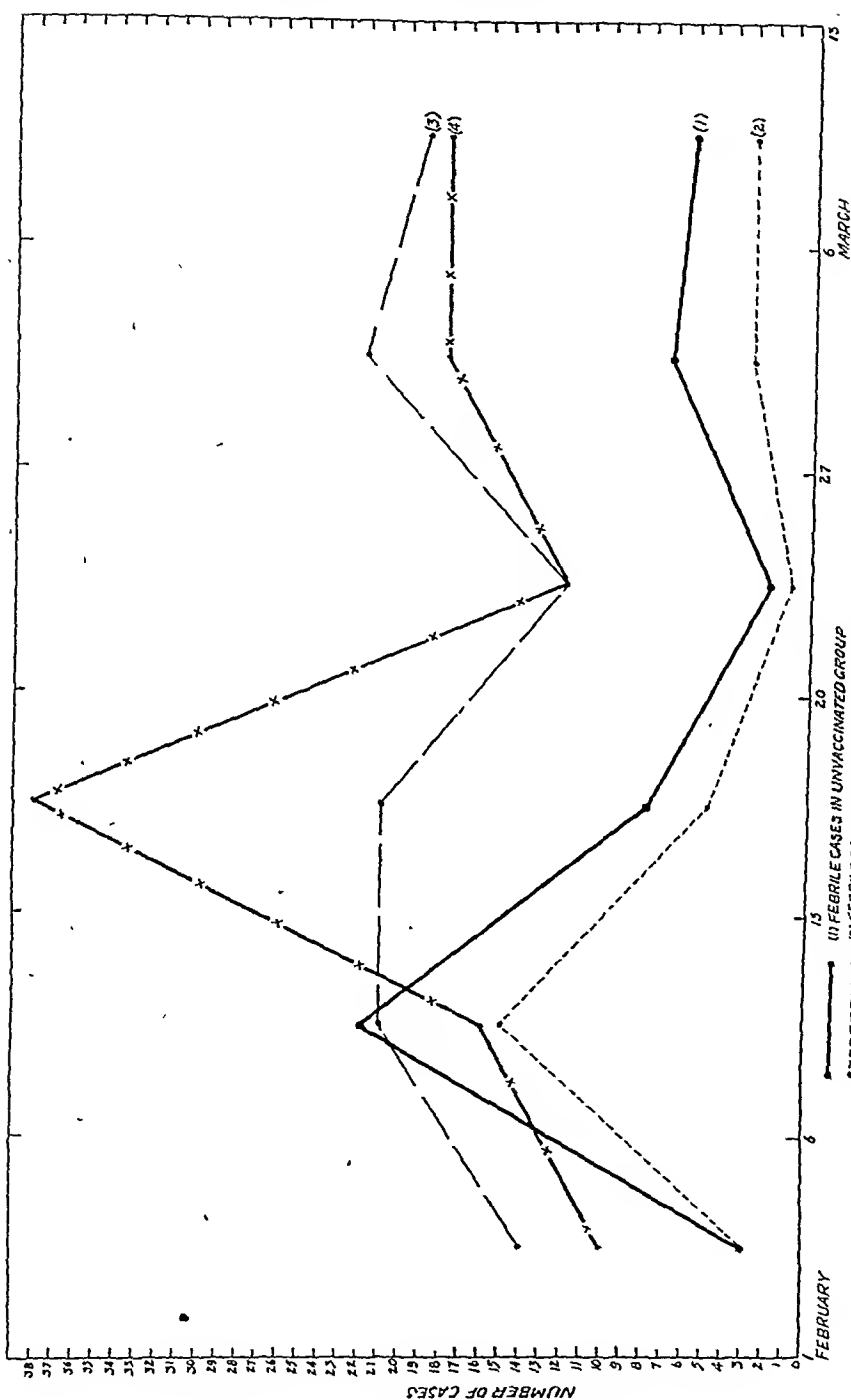


CHART II.—Each point on the graphs represents the total number of cases for each week as shown on the abscissa. For proper comparison the 2 lines for the vaccinated group represent approximately twice the actual incidence of cases, since the unvaccinated group in the colony was approximately twice the size of the vaccinated group.

tions in this colony, while Table 6 gives a comparison of the days of fever and height of fever in the unvaccinated and vaccinated groups. On account of the small number involved, the difference in incidence between the two groups would not be highly significant were it not for the difference in the severity of infection in the two groups. Of those with temperatures of 102° and over there were 26 in the unvaccinated group and only 2 in the vaccinated group. On account of the diminishing supply of ferrets, nasopharyngeal washings were obtained from but one unvaccinated febrile boy (W. M.), and from one vaccinated febrile boy (H. N.), on February 13, 1937. A virus identified as similar to PR-8 was isolated by ferret and mouse passage from the washings of the vaccinated boy. In this epidemic the white cell counts were high for influenza, the large majority being 9000 or above. The obvious possibility, therefore, that secondarily invading bacteria played an important part in this epidemic, must be considered. However, the signs, symptoms and course of the disease in most instances were characteristic of mild epidemic influenza.

TABLE 5.—INCIDENCE OF RESPIRATORY INFECTIONS AT COLONY J., FEBRUARY 1 TO MARCH 13, 1937.

Group.	Number in group.	Febrile.		Afebrile.	
		Cases.	%	Cases.	%
Unvaccinated	357	42	11.8	107	30
Vaccinated	193	13	6.7	57	29.5

TABLE 6.—COMPARISON OF DAYS OF FEVER AND HEIGHT OF FEVER IN TWO GROUPS, COLONY J.

Group.	Total days.	Days per case.	Average per individual.	Cases with 102°-102.8°.	Cases with 103° and over.
Unvaccinated	112	2.66	.31	19	7
Vaccinated	36	2.77	.19	2	0

TABLE 7.—INCIDENCE OF RESPIRATORY INFECTIONS AT COLONY S., FEBRUARY 20 TO APRIL 15, 1937.

Group.	Number in group.	Febrile.		Afebrile.	
		Cases.	%	Cases.	%
Unvaccinated	970	42	4.3	88	9.1
Vaccinated	480	9	1.9	32	6.7

In Colony S. approximately 1450, of whom about one-third were vaccinated, respiratory infections resembling epidemic influenza were limited to a few of the cottages. In Table 7 is recorded the incidence of respiratory infections in this colony from February 20 to April 15, 1937. The first 3 vaccine injections were completed on December 6, 1936, and an additional injection was given on March 14, 1937, since at that time a more rapid spread of the disease was expected from the few cottages already affected. This rapid spread did not occur; but it is of interest that after March 14, 18 febrile respiratory infections occurred in the unvaccinated group and only 2 extremely mild febrile infections occurred in the

vaccinated group. Previous to this period, from February 20, to March 14, 1937, the comparative incidence in same order was 24 to 7. The incidence of afebrile respiratory infections in the two groups during other parts of the year was practically the same, for which reason the difference found during this period of febrile infections would appear to be significant.

A large number of the white cell counts were low, but there were many counts of 10,000 and over. Nasopharyngeal washings were not injected into ferrets chiefly on account of the scarcity of these animals, and for the other reasons mentioned. Probably due to the fact that this colony is more strictly isolated than the others the febrile respiratory infections did not occur until late winter and early spring.

Discussion. The simplest explanation of the results recorded is that man, like other susceptible animals, develops immunity by intramuscular injections of active human influenza virus, the degree of immunity varying inversely with the length of time following vaccination as demonstrated by exposure to the disease. Although obviously the large number of other factors involved do not permit of simple explanations, certain of the data to be mentioned fulfill the requirements of such a hypothesis.

If the epidemic of March, 1936, at Colony N.L. was due chiefly to the human influenza virus, which appears probable, the most solid immunity was afforded when the active human virus was injected intramuscularly in advance of the oncoming epidemic. However, the number in the group vaccinated with human virus was not large (110) nor is it clear why the swine virus (S-15) vaccine appeared to reduce the number of days of fever only and did not reduce the incidence of respiratory infections. It is possible that antigenic differences in the two strains of virus may account for the different responses of susceptible individuals, and that the findings of Magill and Francis³ are applicable primarily to the rabbit or other naturally immune animals. In addition, filtering the mouse-lung vaccine emulsion through Berkefeld filters reduced considerably the potency of the vaccine. More potent swine influenza virus vaccine might have produced a better cross immunity against the human virus disease.

Next in order of efficacy appeared to be the intramuscular vaccinations of the same Colony N.L. ending on December 15, 1936, 36 days before the onset of the influenza epidemic on January 20, 1937, from which the human virus was obtained by passage in ferrets. The marked reduction in incidence of febrile respiratory infections and particularly in days of fever in the vaccinated group rather closely approached the favorable results obtained one year earlier; also the larger number included in the group vaccinated with human virus (275) added to the statistical value of the data. However, in a comparison of these results with others, it must be remembered that most of those included in the vaccinated group

had received either human or swine virus in mouse-lung emulsions intramuscularly in March, 1936, which may have assisted the immunity developed by the more recent vaccination.

In the very small epidemics of Colonies J. and S. is to be noted the least efficacy of the vaccine in protecting those injected and at the same time the longest interval between vaccination and the onsets of the epidemics, namely, 64 days in Colony J. and 76 days in Colony S. Confusing factors in Colony J. were the finding of human influenza virus in nasopharyngeal washings from a vaccinated individual and the generally higher white cell counts of around 9000, an unusual finding for epidemic influenza. For these reasons question has arisen as to whether a different strain of influenza virus was present in Colony J., despite the fact that cross neutralization was obtained with human influenza virus PR-8, and also as to whether bacterial factors played an important or possibly a primary rôle in the epidemic. However, the marked reduction in the height of fever—26 individuals with temperatures of 102° and over in the unvaccinated group as compared to 2 individuals in the vaccinated group—and the moderate reduction in incidence in the vaccinated group as compared to the unvaccinated group suggest that the human influenza virus as a causative agent and the protection afforded by its injection were important factors in these febrile respiratory infections.

However, in all of the epidemics of febrile respiratory infections here recorded, the possibility that bacteria may have been important factors, must be considered. In Colony S. the fact that following an additional injection of vaccine on March 14, 1937, 18 febrile respiratory infections occurred in the unvaccinated group up to April 15, 1937, and but 2 in the vaccinated group from the standpoint of immunity would appear also to favor the importance of a short interval between vaccination and the onset of an epidemic. From March 14 to April 8 no febrile respiratory case occurred among the vaccinated group. However, the comparatively small number of febrile cases in the unvaccinated group lessens the statistical value of this finding.

On the single attempt made, human influenza virus was found in Philadelphia in nasopharyngeal washings from a nurse with typical epidemic influenza. The strains of virus isolated from the different colonies and from Philadelphia, are being studied and the findings concerning them will be reported later. All of the strains showed cross-neutralization with the PR-8 strain of human influenza virus.

In the other 3 colonies vaccinated, V.T., VS. and W., and among a Philadelphia nursing group (120) of whom one-half were vaccinated, there were no significant findings since respiratory infections at no time reached epidemic proportions.

Referring to the simple hypothesis mentioned above, it would appear, therefore, that a considerable degree of immunity to epi-

demic influenza can be produced by intramuscular injections of active human influenza virus, but it is not clear as to whether such immunity is of short or long duration.

Summary. 1. Human beings in 5 large State Colonies and in one private institution were vaccinated intramuscularly with active virus (PR-8) of human influenza, covering the epidemics of respiratory infections of two winters, 1935-1936 and 1936-1937.

2. The method of vaccination is discussed. Approximately one-third of the inmates of each institution was vaccinated. No generalized or marked local reactions occurred from the chick embryo virus cultures used, and there was no evidence of the vaccinations causing any respiratory infections. This was readily determined as the vaccinations were performed at a time when practically no respiratory infections were present in any of the institutions studied.

3. Several epidemics of influenza in Philadelphia and among the institutions are described, from 3 of which human influenza viruses were obtained. All of these viruses showed cross-neutralization with strain PR-8 of human influenza virus.

4. The protection afforded by vaccination with active human influenza virus and the possible importance of the interval between vaccination and the onset of the epidemic, are discussed.

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REFERENCES.

- (1.) Francis, T., Jr., and Magill, T. P.: *J. Exp. Med.*, 63, 655, 1936. (2.) Francis, T., Jr., Magill, T. P., Beck, M. D., and Rickard, E. R.: *Studies with Human Influenza Virus During the Influenza Epidemic of 1936-1937*. (3.) Magill, T. P., and Francis, T., Jr.: *Proc. Soc. Exp. Biol. and Med.*, 35, 463, 1936. (4.) Smith, W., Andrewes, C. H., and Laidlaw, P. P.: *Lancet*, 2, 66, 1933. (5.) Smorodintseff, A. C., et. al.: *AM. J. MED. SCI.* (6.) Stokes, J., Jr., Chenoweth, A. D., Waltz, A. D., Gladen, R. G., and Shaw, D. R.: *J. Clin. Invest.*, 16, 237, 1937.

VASOCONSTRICTOR PROPERTIES OF BENZEDRINE AND ITS USE IN THE RELIEF OF THE COMMON COLD.

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A NUMBER of papers have appeared describing the use of benzedrine in the treatment of the common cold. It is the purpose of the present communication to present a critical study of 59 additional cases and to present pharmacologic evidence regarding the vasoconstrictor properties of this substance.

Bertolet² reported that practically 9 out of 10 cases with nasal congestion obtained some relief from the use of benzedrine, the result being excellent in one-quarter of his patients. This result was confirmed by Byrne⁴ who noted in addition that it was of no value in patients with an underlying sinusitis. Scarano^{9a} found benzedrine and ephedrine about equally efficacious in relieving nasal congestion which was confirmed by Giordano;⁶ Scarano^{9b} in a later paper presented drawings clearly illustrating the shrinkage effected by benzedrine. Sulman¹⁰ stated in addition that benzedrine not only controlled congestion but he believed it caused abortion of colds and prevented the occurrence of further colds in susceptible patients.

Benzedrine (benzyl-methyl-carbinamine or β -phenylisopropylamine), a volatile synthetic sympathomimetic substance more closely allied structurally to ephedrine than to epinephrine, was studied by Pines, Miller and Alles⁸ in 1931. Benzedrine is less closely related structurally and pharmacologically to epinephrine than the new synthetic substance meta-synephrin or neo-synephrin.³

Clinical Study. Benzedrine* was dispensed as an inhaler to over 200 students at the University Clinic upon whom a diagnosis had been made of acute or vasomotor rhinitis. Each student was instructed to inhale once through each nostril not more frequently than every hour. Records were kept separately of the average number of colds per year, their average duration and usual treatment, the effect of benzedrine upon the symptoms and duration of the cold so treated and other relevant data. Some of the students failed to report the results and data in other cases had to be excluded because they were incomplete or unreliable.

Of 59 cases with satisfactory data, only 3 reported no relief whatsoever of symptoms; 16 recorded the result as fair, 27 as good and 13 as excellent. These figures appear to confirm the efficacy of the substance, but there remained a suspicion that many of the students who failed to report again did so because the treatment had not been beneficial. Whether or not this be true, the results are in agreement with those previously recorded and indicates that benzedrine is of considerable value in relieving nasal congestion.

Each of the patients treated suffered from an average of approximately 4 colds per year and each cold lasted an average of about 9 days. In contrast, 27 further students who stated that they were relatively free of colds had an average of 2 colds per year lasting 4 days each. The group under treatment was thus definitely susceptible to colds. While benzedrine was efficient in relieving nasal congestion, it had practically no effect on the average duration of the colds. In the treated group, previous colds had lasted a mean of 8.7 days each, while the average duration of the cold treated with benzedrine was 8.1 days.

* Benzedrine inhalers and benzedrine sulphate used in the present investigation were supplied to us by the Smith, Kline & French Laboratories of Philadelphia, and ephedrine hydrochloride used for comparative purposes by the Abbott Laboratories of Montreal.

The Toxicity of Benzedrine Sulphate to Mucosal Surfaces. The toxicity of benzedrine has been studied by Hartung and Munch,⁷ Ehrich and Krumbhaar,⁵ and Alles¹ who determined the minimum lethal dose in rats and guinea pigs. There is no experimental evidence regarding the toxicity or relative toxicity of benzedrine toward mucosal surfaces which was the information more particularly required in the present study. This was obtained by comparing the relative effects of benzedrine, ephedrine and epinephrine on the activity of cilia in the mucosa lining the esophagus of the frog. Pithed frogs were pinned on their backs, the lower jaw removed, the esophagus split, the mucosa gently washed with saline and a light mustard seed allowed to be carried by the cilia over a measured distance of the ciliated surface. The length of time in seconds required for this was determined repeatedly until consistent readings were obtained and then the mucosa was gently washed with 0.1% benzedrine sulphate or 0.1% ephedrine hydrochloride or 0.1% epinephrine hydrochloride and the process repeated. Two dozen frogs were used to determine the effect of each drug.

TABLE 1.—THE EFFECT OF BENZEDRINE, EPHEDRINE AND EPINEPHRINE UPON THE NUMBER OF SECONDS REQUIRED BY CILIA IN THE ESOPHAGEAL MUCOSA OF THE FROG TO CARRY A SEED A GIVEN DISTANCE.

Value.	Solution applied (0.1%).								
	Benzedrine.			Ephedrine.			Epinephrine.		
	Before.	After.	Difference.	Before.	After.	Difference.	Before.	After.	Difference.
Minimum* . .	13	19	- 6	12	14	-20	18	20	-25
Maximum* . .	80	125	+94	60	100	+50	75	115	+50
Mean	34	52	+18	34	43	+10	40	43	+ 3
Standard deviation	14	24	21	12	21	15	16	29	22

* The minimum and maximum values are for each column and hence the "difference" values do not necessarily represent the difference between the preceding values in the line.

The results obtained have been depicted in Table 1. The values given include the shortest interval required to carry the mustard seed the given distance, the longest interval, the mean interval and the standard deviation of the mean. In 18 of 22 frogs (82%) application of 0.1% benzedrine sulphate produced slowing of ciliary motion, the rate being on the average 65% of that previous to the application of the drug. On the other hand, similar concentrations of ephedrine hydrochloride and epinephrine hydrochloride had no consistent effects upon ciliary motion. On the average, the rate was slightly slower with each of the latter drugs but in both instances there were just about as many frogs which exhibited increased as decreased rates. It may be concluded that benzedrine sulphate is slightly more toxic to ciliary motion than ephedrine or epinephrine hydrochlorides.

The Vasoconstrictor Properties of Benzedrine Sulphate. Experiments were performed in an effort to ascertain the site at which benzedrine produces vasoconstriction and also to compare its power of vasoconstriction with that of ephedrine and epinephrine. One-

half cc. of 0.01% of the respective salts of each of these substances was injected into the peripheral circulation of frogs perfused with Ringer's solution in the usual manner. In 12 of 15 frogs, benzedrine sulphate caused the rate of flow of the perfusate to diminish, the average maximum constriction produced in each frog being 34%. A similar dose of ephedrine hydrochloride had practically the same effect, the average maximum constriction being 31%. Epinephrine produced constriction in all experiments and the average maximum constriction was 49%. Benzedrine is thus about as efficient as ephedrine but less so than epinephrine in its vasoconstriction of the peripheral vessels of the frog.

When the same dose of epinephrine hydrochloride was introduced into ergotaminized frogs, vasodilatation occurred in 9 out of 10 animals, the average maximal increase in the rate of flow of the perfusate being 105%. Under the same conditions, benzedrine sulphate produced an increase of 114%. Hence it may be concluded that benzedrine acts upon the motor sympathetic endings in the blood-vessels of the frog. From experiments upon cocainized frogs it was found that the mechanism of this action is not the same as that of epinephrine. A dose of 0.5 cc. of 0.01% epinephrine hydrochloride produced an average maximum constriction of 79% in cocainized frogs, cocaine sensitization being evidenced by all of the animals. But cocaine had no effect on the vasoconstrictor properties of benzedrine sulphate.

Benzedrine was less efficient than epinephrine and about equal to ephedrine in raising the blood pressure of rabbits anesthetized with urethane and ether. Eight animals were used and a dose of 1 cc. of 0.005% of the respective salts was injected intravenously on repeated occasions. The average maximal increase in blood pressure with epinephrine was 160%, with ephedrine 77% and with benzedrine 71%. The average blood pressure before injecting epinephrine was 50 mm. of mercury and after it the average maximum blood pressure was 130; before ephedrine the average was 48 mm. and after, 85; before benzedrine the average was 38 and after, 65. The average duration of the complete effect of epinephrine was 159 seconds, of ephedrine 91 seconds and of benzedrine 71 seconds. The effect of benzedrine was not as consistent as that of either of the other two substances; the first dose given an animal usually produced a well-marked rise in blood pressure but subsequent doses usually had less effect.

Previous cocainization enhanced the effect of epinephrine on the blood pressure of rabbits, but actually decreased the response to ephedrine and benzedrine. From 10 experiments with each drug, epinephrine immediately after cocainization produced a mean maximal increase in blood pressure of 203%, ephedrine of 3.5% and benzedrine of 17%. In a number of instances a fall in blood pressure occurred on injecting ephedrine or benzedrine after cocaine. Previous ergotaminization diminished but did not reverse the effect

of ephedrine and benzedrine; the average maximum rise in blood pressure produced by the same dose of benzedrine sulphate in 7 ergotaminized rabbits was 17% and of ephedrine hydrochloride 10%. Hence benzedrine, like ephedrine, acts on the motor sympathetic endings in rabbit vessels but not in a manner identical to that of epinephrine and in addition it must act to a certain extent directly on the muscle since some constriction occurred in ergotaminized animals.

Conclusions. 1. From clinical studies on the topical application of benzedrine in the relief of the common cold, it appears that benzedrine relieves symptoms resulting from nasal turgescence but does not shorten the duration of the cold. Water soluble benzedrine sulphate is more toxic to the mucosa than either ephedrine or epinephrine though not greatly so.

2. From pharmacologic studies on frogs and rabbits, it appears that benzedrine acts by stimulation of the motor sympathetic endings in the vessel wall but not in the same manner as epinephrine and in addition probably acts to a certain extent directly upon the smooth muscle. In this vasoconstrictor property it is about as efficacious as ephedrine but less so than epinephrine.

REFERENCES.

- (1.) Alles, G. A.: *J. Pharm. and Exp. Therap.*, 47, 339, 1933. (2.) Bertolet, J. A.: *Med. J. and Rec.*, 136, 75, 1932. (3.) Boyd, E. M.: *J. Pharm. and Exp. Therap.*, 60, 174, 1937. (4.) Byrne, H. V.: *New England J. Med.*, 209, 1048, 1933. (5.) Ehrich, W. E., and Krumbhaar, E. B.: *Ann. Int. Med.*, 10, 1874, 1937. (6.) Giordano, A. A. S.: *Penna. Med. J.*, 39, 20, 1935. (7.) Hartung, W. H., and Munch, J. C.: *J. Am. Chem. Soc.*, 53, 1875, 1931. (8.) Pines, G., Miller, H., and Alles, G. A.: *J. Am. Med. Assn.*, 94, 790, 1930. (9.) Scarano, J. A.: (a) *Med. Rec.*, 140, 802, 1934; (b) *Ibid.*, 143, 161, 1936. (10.) Sulman, L. D.: *Med. Times and Long Island Med. J.*, 63, 374, 1935.

OBSERVATIONS ON THE ETIOLOGY OF THE TOXEMIAS OF PREGNANCY.

II. PRODUCTION OF ACUTE EXACERBATION OF TOXEMIA BY SODIUM SALTS IN PREGNANT WOMEN WITH HYPOPROTEINEMIA.*

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THE designation "toxemia of pregnancy" has included at one time or another almost all the non-septic, non-mechanical ills of the gravid state. At the present time certain of these conditions, such as the

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anemias⁷ and the polyneuritis⁸ of pregnancy, are regarded as due to nutritional deficiency. It has also become apparent that the diagnosis "toxemia of pregnancy" has in the past included such conditions as essential hypertension, acute and chronic glomerulonephritis, pyelonephritis, and rarely malignant nephrosclerosis. In fact, probably five-sixths of patients said to have "toxemia" of pregnancy are suffering from some independent and frequently pre-existing disease in which the pregnancy is merely an incident. Nevertheless there remains a group of patients who have been apparently well prior to pregnancy and who exhibit no evident abnormalities after the puerperium, but who do develop relatively acute arterial hypertension in the last trimester of pregnancy, and who do not exhibit the clinical or laboratory findings of glomerulonephritis, pyelonephritis, or malignant nephrosclerosis. These patients have been shown to have markedly diminished plasma proteins invariably associated with water retention.^{6a,b} The condition has usually been designated "low reserve kidney," "pre-eclampsia," or "eclampsia," depending on the severity of the condition.⁵ Lastly there are patients with pre-existing arterial or renal disease in whom the development of increasing hypertension or albuminuria is associated with hypoproteinemia and water retention.

The studies to be reported here indicate that hypoproteinemia is the primary factor permitting significant water retention in pregnancy and that such retention may be accompanied by considerable rises in blood pressure, increasing albuminuria and the appearance of such pre-eclamptic manifestations as severe headache, visual disturbances, and vertigo. It is known that the administration of sodium salts to normal individuals may produce slight increments of water retention, whereas in individuals with lowered plasma proteins marked retention may occur in inverse proportion to the plasma protein level.⁴ There is evidence that the bicarbonate is more effective than the chloride of sodium in inducing water retention.⁴ The mechanism by which sodium salts produce water retention is a complicated one. For a thorough discussion of this problem Peters' "Body Water"³ may be consulted.

Methods. Women in the last trimester of pregnancy were admitted to the Thorndike Ward of the Boston City Hospital, but *not* put to bed. Each patient received the usual ward diet. Fluids were allowed *ad libitum*. The patients were not encouraged either to increase or decrease their fluid intake. Each patient was weighed upon arising in the morning. About 2 hours after breakfast, the patient having been in a chair for at least 20 minutes, the blood pressure was measured. The daily fluid intake and output were recorded. On the morning after admission to the hospital and at intervals thereafter 20 cc. of blood were withdrawn without stasis from an antecubital vein for analysis. The patients were recumbent for $\frac{1}{2}$ hour prior to this procedure. The 24-hour urine was analyzed daily for albumin by the quantitative method of Tsuchiya. The total plasma protein and the plasma albumin were determined by a micromodification of Howe's method.² In the tables, the "initial" blood pressure represents the *average* of the first

3 days' readings. The change in blood pressure recorded represents the difference between this average and the *average* of the three readings obtained on the mornings of the last 2 days of the test period and that of the morning after the test period. The "initial" weight represents the reading on the day the test period began. The change in weight represents the difference between this weight and that recorded on the first morning after the test period.

TABLE 1.—RESPONSE TO THE ADMINISTRATION OF SODIUM SALTS FOR 7 DAYS IN 8 PREGNANT WOMEN WITH PLASMA COLLOID OSMOTIC PRESSURES ABOVE 220 MM. H₂O.

Case No.	Weight gain.	Blood pressure change.		Highest blood pressure prior to admission.		Average "initial" blood pressure.		Change in albuminuria.	Average daily fluid exchange during test period.		Calculated plasma oncotic pressure.
	%	mm. Hg.		mm. Hg.		mm. Hg.			Intake cc.	Output cc.	mm. H ₂ O.
		Diast.	Syst.	Syst.	Diast.	Syst.	Diast.				
1	0	-6	-19	154	70	125	74	0	2597	2057	230
2	0	-3	0	145	90	138	83	0	2622	1630	255
3	0.8	+3	+2	170	96	130	77	0	1440	1514	250
4	1.2	+1	+19	184	118	124	87	0	3030	3026	248
5	1.4	-4	-11	146	90	119	86	0	2391	1093	260
6	1.6	+1	-18	220	110	198	100	0	3214	1855	225
7	1.8	-2	-2	184	118	139	91	0	2468	3063	230
8	1.8	+1	0	150	100	135	85	0	2760	1470	252
Av.	1.1	-1	-3	169	99	138	85	0	2565	1963	244

Case 6 received sodium bicarbonate.

Observations. I. Eight women known to have had some degree of arterial hypertension either before or early in pregnancy were studied in the last trimester of pregnancy. The osmotic pressure of the plasma proteins, calculated by the method of Wells, Youmans and Miller, varied from 230 to 260 mm. of water (Table 1). None of these women had significant albuminuria. In practically every instance the initial average blood pressures recorded in the table are lower than those recorded prior to admission to the hospital. Why hospitalization without bed rest should result in a fall in blood pressure is not for discussion here.

On the third morning of their hospital stay 7 of these women commenced receiving 16 gm. of sodium chloride (= 6.3 gm. of Na) daily, and one (Case 6)-commenced taking 23 gm. of sodium bicarbonate (= 6.3 gm. of Na) daily for a minimum period of one week. Gains of weight up to 1.8% of the initial body weight were observed (Table 1). None developed visible edema. No significant changes in diastolic blood pressure occurred (Table 1). In no instance did albuminuria increase nor did cylindruria or hematuria appear. No subjective symptoms occurred. Observations in two typical cases are charted (Charts I and II).

It thus appears that the daily administration of 6.3 gm. of sodium (either in the form of 16 gm. of sodium chloride or 23 gm. of sodium bicarbonate) results in small increments of weight, but is without other

effect on women with arterial hypertension in the last trimester of pregnancy who have essentially normal plasma protein values.

TABLE 2.—RESPONSE TO THE ADMINISTRATION OF SODIUM SALTS FOR 7 DAYS IN 10 PREGNANT WOMEN WITH PLASMA COLLOID OSMOTIC PRESSURES BELOW 220 MM. H₂O.

Case No.	Weight gain.	Blood pressure change.		Highest blood pressure prior to admission.		Average "initial" blood pressure.		Change in albuminuria.	Average daily fluid exchange during test period.		Calculated plasma oncotic pressure.
	%	mm. Hg.		mm. Hg.		mm. Hg.			Intake cc.	Output cc.	mm. H ₂ O.
		Diast.	Syst.	Syst.	Diast.	Syst.	Diast.				
11	{2.5 3.4	- 1 + 6	-10 +15	125 135	85 86	123 125	78 89	0 0	2648 3031	2052 2633	172-207 217-209
12	3.3	+16	+14	182	108	133	79	0	2091	2090	200
13	3.6	+ 5	+ 3	184	106	147	81	0	4160	3820	212
14	4.7	+27	+31	142	84	131	82	+	2391	2585	192
15	4.8	+24	+30	154	100	136	90	0	3906	2320	210
16	5.5	+33	+11	162	100	135	80	+	6266	6253	193*
17	5.7	+12	+16	170	120	135	100	+	1920	1593	182*
18	5.9	+16	+ 7	165	90	128	75	0	2663	1335	180
19	7.2	+ 9	+ 7	150	100	144	92	+	3060	947	212
20	7.7	+ 6	+17	144	100	135	108	+	4185	2250	120*
Av.	4.9	+14	+14	156	98	131	86		3320	2524	192

* The test period was limited to 4 days or less in Cases 16, 17, 20 because of the development of pre-eclamptic symptoms.

The test period in Case 15 was limited to 5 days because of severe headache.

Cases 11, 14, 18, 19 received sodium bicarbonate; Cases 11 had 3 test periods (Chart IX); Case 12 had arterial hypertension prior to the pregnancy; Case 13 had chronic nephritis prior to the pregnancy.

TABLE 3.—RESPONSE TO THE FEEDING OF A HIGH PROTEIN DIET TO 6 PREGNANT WOMEN WITH PLASMA COLLOID OSMOTIC PRESSURES BELOW 220 MM. H₂O.

Case No.	Weight loss.	Blood pressure change.		Highest blood pressure prior to admission.		Average "initial" blood pressure.		Change in albuminuria.	Average daily fluid exchange during test period.		Calculated plasma oncotic pressure.
	%	mm. Hg.		mm. Hg.		mm. Hg.			Intake cc.	Output cc.	mm. H ₂ O.
		Diast.	Syst.	Syst.	Diast.	Syst.	Diast.				
31	2.9	-2	- 9	160	108	148	90	0	2562	1935	206
32	3.4	-5	-19	150	102	128	85	0	2371	1250	205
33	3.4	+3	- 3	170	110	143	87	0	3002	2735	218
34	3.7	-9	- 9	168	104	143	95	0	2334	2281	220
35	3.8	-5	- 8	160	120	136	100	0	2540	2544	210
36	4.1	-6	- 8	166	100	157	96	0	2880	2985	204
Av.	3.5	-4	- 8	162	107	142	92	0	2614	2288	210

II. Ten women were studied in the last trimester of pregnancy. All of them had some degree of arterial hypertension and 8 were known to have had normal blood pressures before or early in pregnancy. One patient had definite evidence of having essential hypertension and another chronic glomerulo- or pyelonephritis prior to pregnancy. The osmotic pressure of the plasma proteins, calculated as above, varied from 120 to 217 mm. of water. Five

patients showed albuminuria of from 0.3 to 2.8 gm. per liter. None had hematuria. On the third morning of their hospital stay 6 commenced receiving 16 gm. of sodium chloride (= 6.3 gm. of Na)

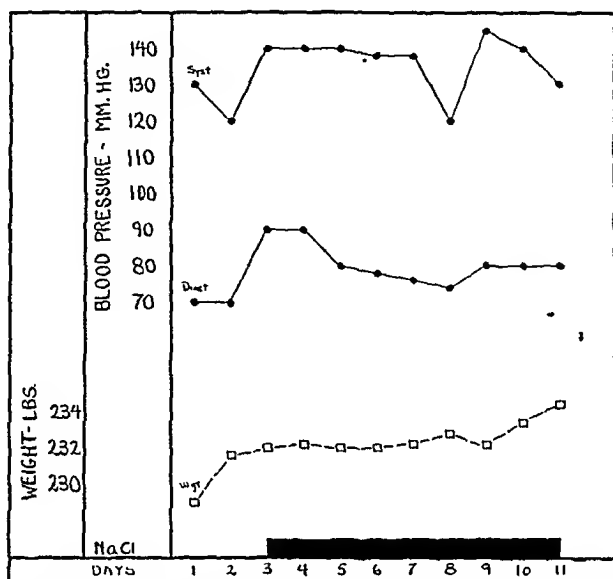


CHART I.—Weight and blood pressure changes in Case 3. Plasma oncotic pressure 250 mm. H₂O. Sodium chloride 16 gm. daily (solid block).

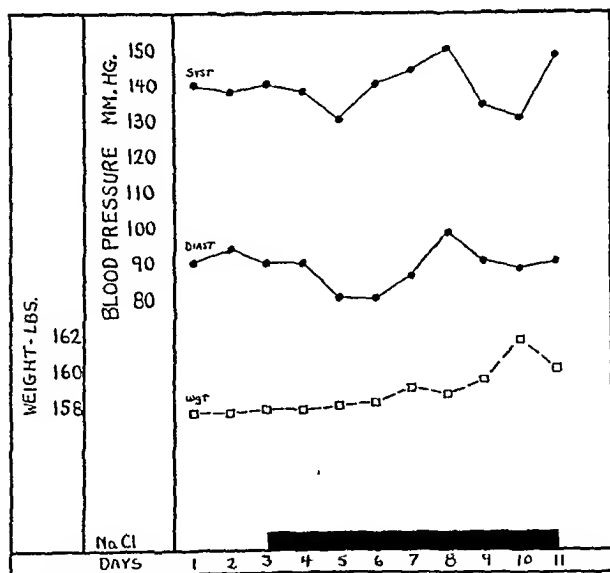


CHART II.—Case 7. Plasma oncotic pressure 230 mm. H₂O. Sodium chloride 16 gm daily (solid block).

and 4 commenced taking 23 gm. of sodium bicarbonate (= 6.3 gm. of Na) daily. Gains in weight of from 2.5 to 7.7% of the initial weight occurred, associated in each instance with the appearance of

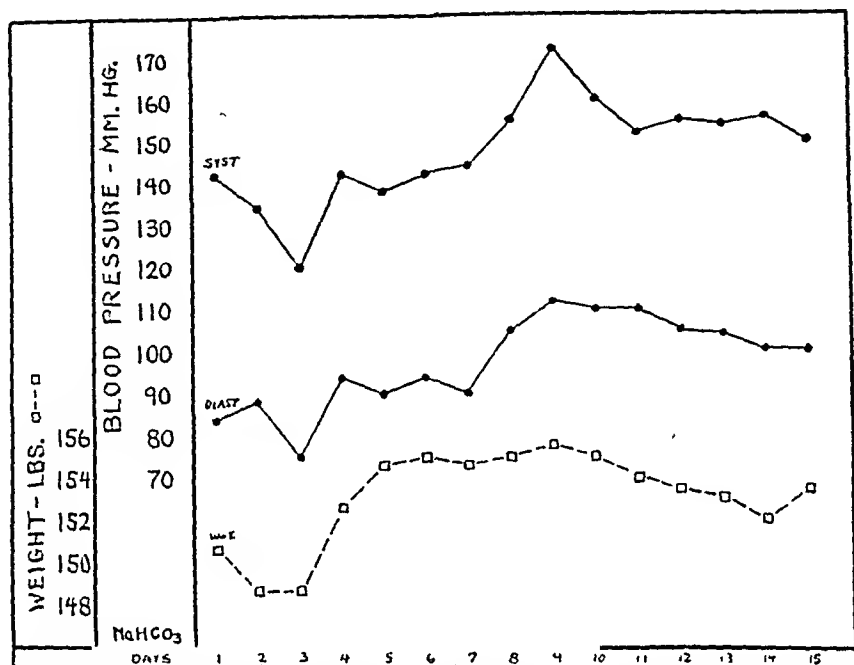


CHART III.—Case 14. Plasma oncotic pressure 192 mm. H_2O . Sodium bicarbonate 23 gm. daily (solid block).

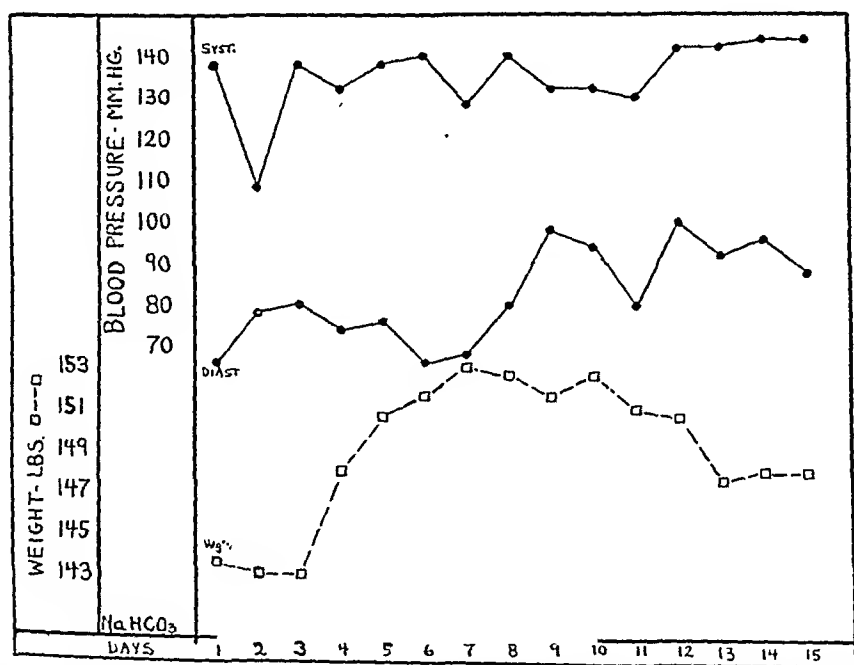


CHART IV.—Case 18. Plasma oncotic pressure 180 mm. H_2O . Sodium bicarbonate 23 gm. daily (solid block).

visible edema involving the extremities and frequently the face. Nine of the 10 women showed an elevation of arterial blood pressure, the diastolic being more consistently affected (Table 2) (Charts III to IX). Five showed significant increases in albuminuria so that the albumin varied from 1 to 5 gm. per liter. Cylindruria occurred in 2 patients and microscopic hematuria in one. In 2 patients the development of severe headache, visual disturbances, and vertigo necessitated the omission of sodium after 3 days (Charts VI and VII). A third patient was so uncomfortable from severe headache and edema that therapy was omitted on the fourth day (Chart VIII), and in a fourth, severe headache necessitated the omission of sodium after 5 days (Chart V).

It is thus apparent that the daily administration of 6.3 gm. of sodium (either in the form of 16 gm. of sodium chloride or 23 gm. of sodium bicarbonate) results in significant gains of weight together with the appearance of visible edema in women with hypoproteinemia during the last trimester of pregnancy. In these women significant rises of arterial blood pressure occurred. In 5 albuminuria increased, and in 3 symptoms of pre-eclampsia appeared necessitating immediate cessation of the sodium administration.

One patient, Case 11 (Chart IX), had 3 test periods. During the first period, when her calculated oncotic pressure was 172 mm. of water, she received 16 gm. of sodium chloride daily for 9 days. Her weight increased slowly by 2.5%. The blood pressure was unchanged. During the next 6 days she received 23 gm. of sodium bicarbonate daily. Her weight increased slowly by an additional 1.5%. No change in blood pressure occurred. At the end of this period her plasma proteins had risen so that the calculated oncotic pressure was 207 mm. of water. One month later she was readmitted to the hospital with plasma proteins giving a calculated oncotic pressure of 217 mm. of water. At this time she was given 23 gm. of sodium bicarbonate daily. Her weight increased by 3.4% in 2 days, edema appeared, and her blood pressure rose from an average of 125 systolic and 89 diastolic to 140 systolic and 95 diastolic (Chart IX). However, during the continued administration of sodium her weight declined to its original level, edema disappeared, and concomitant with this her blood pressure fell to an average of 126 systolic and 74 diastolic.

This phenomenon of spontaneous diuresis and loss of edema during the continuous administration of sodium salts has been observed in patients with hypoproteinemia due to malnutrition or nephrosis and in animals subjected to plasmapheresis as well as those with nutritional hypoproteinemia.¹ No satisfactory explanation for this has been suggested.

III. Five patients of Group II were given ammonium chloride daily. One (Case 16) received 16 gm. daily 4 days after the omission of sodium chloride (Chart VI) for a period of 4 days during which

time she lost 3.5% of her body weight and her blood pressure fell from an average of 146 systolic and 103 diastolic to 125 systolic and 70 diastolic.

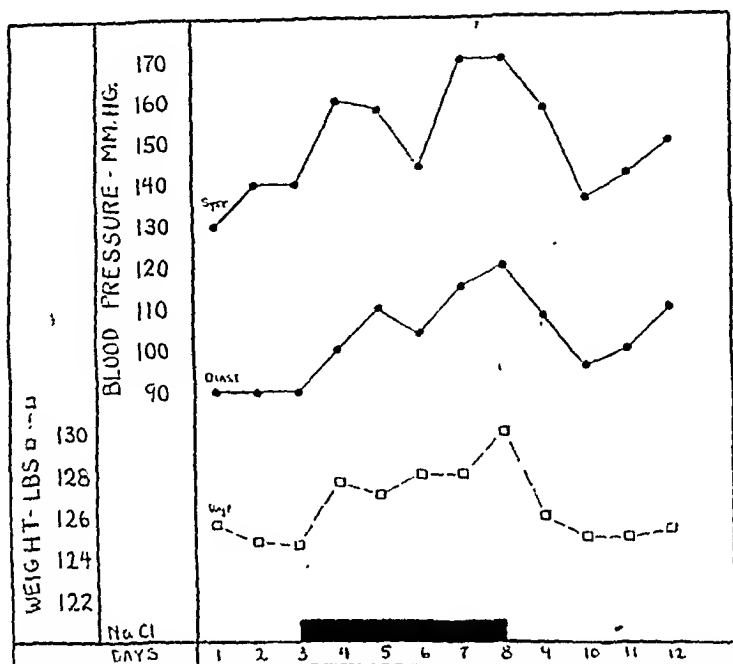


CHART V.—Case 15. Plasma oncotic pressure 210 mm. H_2O . Sodium chloride 16 gm. daily (solid block).

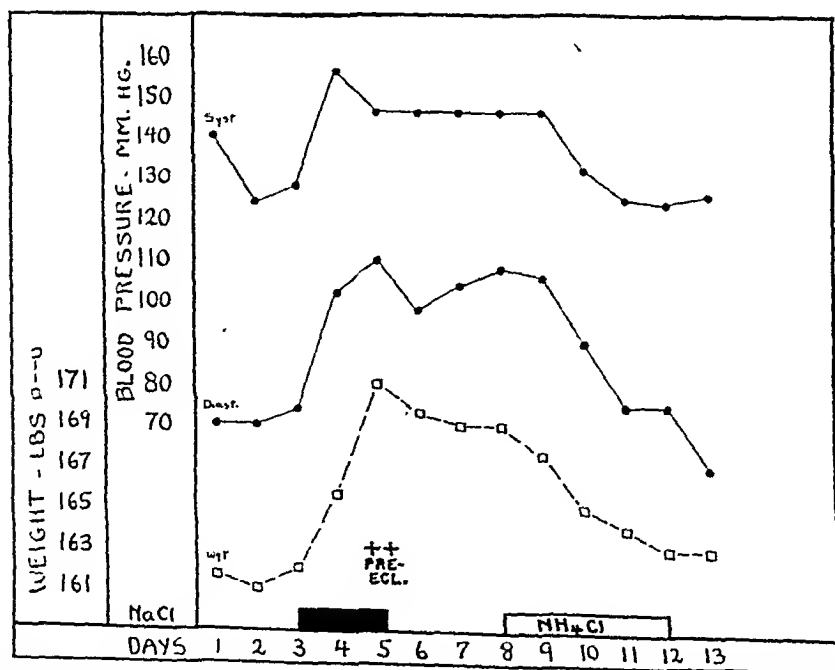


CHART VI.—Case 16. Plasma oncotic pressure 193 mm. H_2O . Sodium chloride 16 gm. daily for 2½ days (solid block). Ammonium chloride 16 gm. daily for 4 days (open block).

The second patient (Case 17) received 16 gm. of ammonium chloride daily for 6 days, 3 days after admission to the hospital

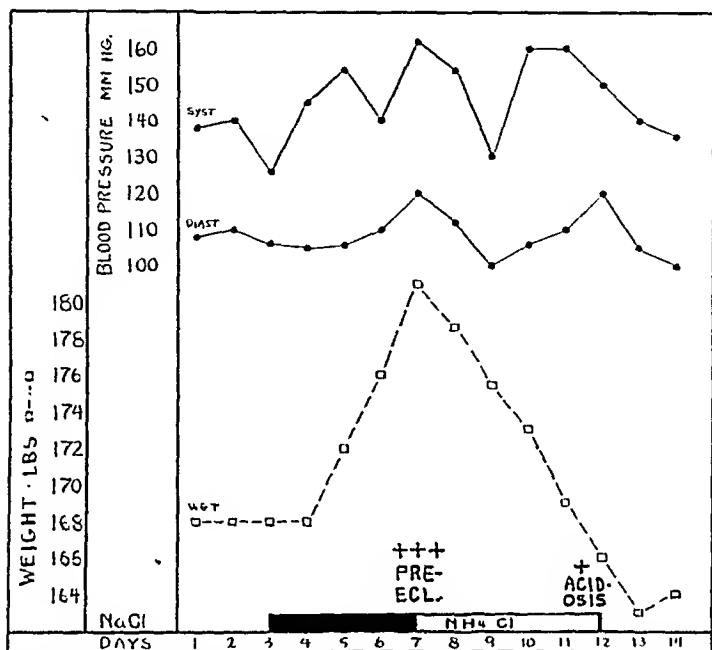


CHART VII.—Case 20. Plasma oncotic pressure 120 mm. H₂O. Sodium chloride 16 gm. daily for 4 days (solid block). Ammonium chloride 8 gm. daily for 5 days (open block).

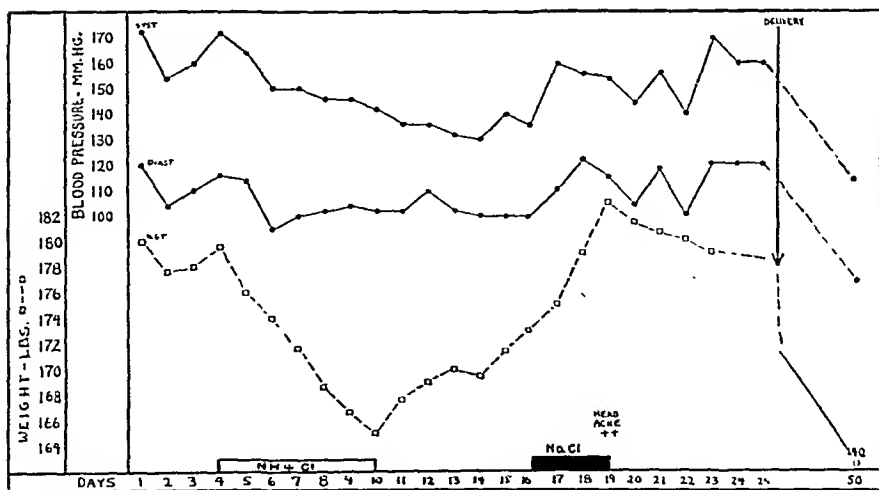


CHART VIII.—Case 17. Plasma oncotic pressure 182 mm. H₂O. Ammonium chloride 16 gm. daily for 6 days (open block). Sodium chloride 16 gm. daily for 3 days (solid block).

(Chart VIII). Her weight dropped by 8.1% in 6 days and her blood pressure fell from an average of 166 systolic and 110 diastolic to 144 systolic and 102 diastolic.

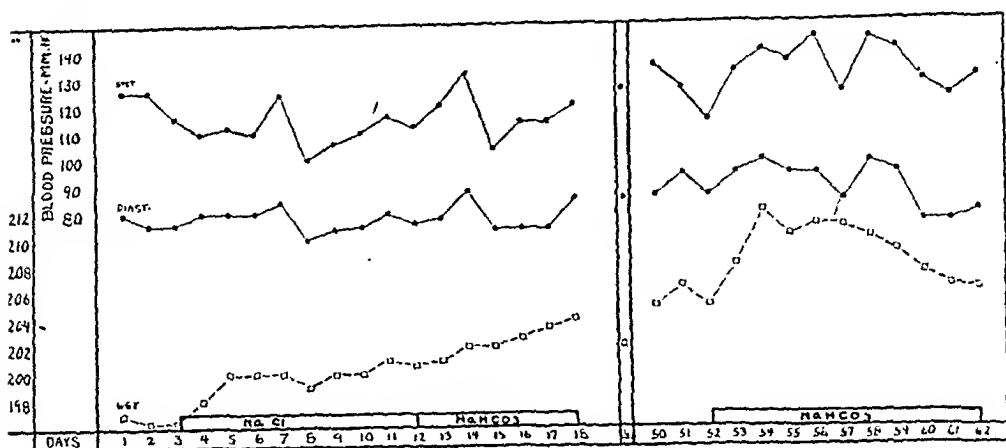


CHART IX.—Case 11. Plasma oncotic pressure 172 to 217 mm. H_2O . Sodium chloride 16 gm. daily for 9 days. Sodium bicarbonate 23 gm. daily for 6 and 10 days in second and third periods.

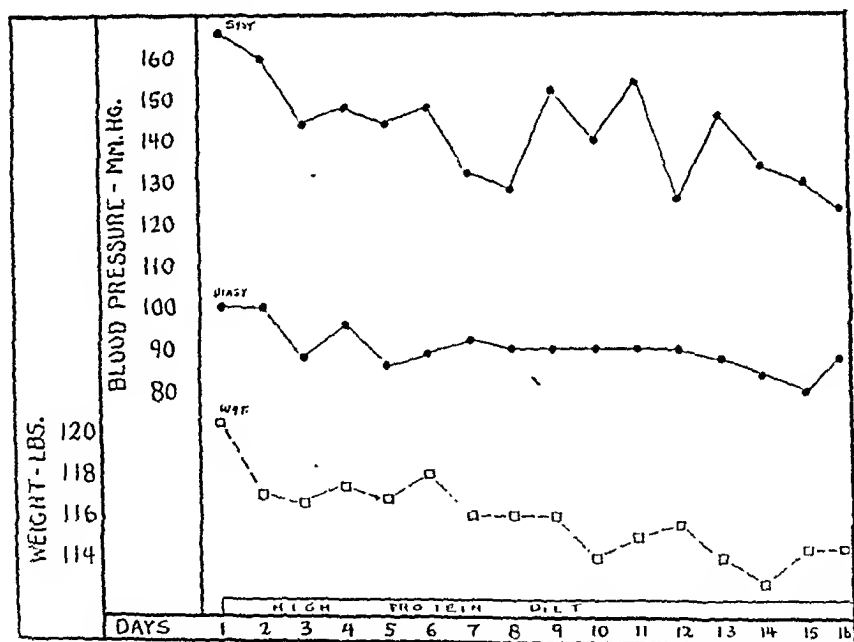


CHART X.—Case 36. Plasma oncotic pressure 204 mm. H_2O . 260 gm. protein diet for 16 days.

The third patient (Case 20) received 8 gm. of ammonium chloride daily immediately after pre-eclamptic symptoms had been produced by sodium chloride (Chart VII). Acidosis occurred after 4 days with hyperpnea, dyspnea, dehydration, and nausea. Her weight fell by 9.9% and her blood pressure decreased from an average of 152 systolic and 112 diastolic to 142 systolic and 108 diastolic.

Two other patients (Cases 13 and 14) were unable to tolerate ammonium chloride due to the occurrence of nausea, vomiting, and acidosis within 48 hours of its first administration.

Four patients, in addition to the 24 referred to above, with normal blood pressures in the last trimester of pregnancy, received 16 gm. of ammonium chloride daily for 1 week. Weight losses of 4.6, 5.0, 5.7, and 5.8% occurred. There were no consistent blood pressure changes.

IV. It is remotely possible that the 10 women with hypoproteinemia would have developed the changes recorded even if sodium had not been administered. Accordingly, 6 other women, whose condition was comparable to the 10 of Group II, with calculated plasma oncotic pressures varying from 206 to 220 mm. of water, were placed on a daily diet consisting of 260 gm. of protein, 100 gm. of carbohydrate, and 50 gm. of fat immediately upon admission to the hospital. No sodium other than that contained in the food or taken as seasoning on the food was administered. It is apparent from Table 3 that no significant change occurred in blood pressure or albuminuria. Rather than gains in weight, weight losses of from 2.9 to 4.1% occurred in 1 week's time. In no case did symptoms appear to become worse. A typical case has been charted (Chart X).

Discussion. It is generally conceded that only women who gain weight excessively during pregnancy develop the signs and symptoms of true "toxemia."⁵ Previously⁶ evidence was presented which suggested that this excessive gain in weight was the result of water retention with either occult or gross edema. Further it was indicated that this water retention resulted not from hormonal influences or renal disease, but was the simple effect of lowered oncotic pressure of the plasma proteins. It was also shown that concomitant with a loss of retained water following the administration of a high protein diet the signs and symptoms of "toxemia" abated. In the present study, it has been shown that water retention may be induced in pregnant women, as in non-pregnant subjects, by the administration of sodium salts, and that the degree of retention varies inversely with the oncotic pressure of the plasma proteins. The difference in behavior of women with low oncotic pressures and those with normal pressures is quantitative rather than qualitative insofar as water retention is concerned. It has further been shown that pregnant women with low plasma proteins, who exhibited rapid and marked water retention following the administration of sodium salts, concomitantly developed rises in arterial blood pressure, and in 5 instances increased albuminuria. In 3 of the 10 cases studied symptoms and signs of "pre-eclampsia" appeared. With our present state of knowledge concerning the nature of arterial hypertension it would be foolhardy to speculate on the mechanism involved in producing the hypertension in the pregnant women studied. The fact remains that rapid gains in weight were accompanied by rises in arterial blood pressure.

In previous papers,^{6a,b} it was indicated that lowered plasma proteins could result from a variety of factors, such as poor protein intake, protein loss, and malabsorption, and possibly failure of protein manufacture—all in the presence of the fetal demand for protein building materials. The importance of preventing the operation of the first factor by supplying an adequate amount of dietary protein to all pregnant women has been pointed out.

Summary and Conclusions. 1. Sodium given to 10 pregnant women with hypertension and hypoproteinemia resulted in significant weight gains, the occurrence of visible edema, and rises in the arterial blood pressure in each instance. In 5 women albuminuria increased and in 3 symptoms of pre-eclampsia appeared.

2. An identical amount of sodium given to 8 pregnant women with hypertension but no hypoproteinemia resulted in small increments of weight but was without other effect.

3. Ammonium chloride given to 3, and a high protein diet to 6, pregnant women with hypertension and hypoproteinemia resulted in significant weight losses and declines in arterial blood pressure.

4. The evidence presented suggests that the manifestations of "toxemia" of pregnancy in the patients studied resulted from water retention conditional upon hypoproteinemia.

5. The administration of sodium is dangerous in pregnant women with hypoproteinemia. The bicarbonate is fully as dangerous as the chloride. Its indiscriminate use in pregnancy is contraindicated.

The writer is indebted to Dr. F. H. L. Taylor and Miss Margaret Adams for carrying out the chemical determinations reported in this paper.

This work was made possible through the coöperation of the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital, to whom the writer acknowledges his indebtedness.

REFERENCES.

- (1.) Hastings, A. B., Liu, S. H., and Dieuaide, F. R.: *J. Clin. Invest.*, 10, 683, 1931.
- (2.) Howe, P. E.: *J. Biol. Chem.*, 49, 109, 1921. (3.) Peters, J. P.: *Body Water. The Exchange of Fluids in Man*, Springfield, Ill., Charles C Thomas Company, 1935.
- (4.) Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry I. Interpretations*, Baltimore, The Williams & Wilkins Company, 1932. (5.) Stander, H. J.: *Medicine*, 8, 1, 1929. (6.) Strauss, M. B.: (a) *J. Clin. Invest.*, 14, 710, 1935; (b) *Am. J. Med. Sci.*, 190, 811, 1935. (7.) Strauss, M. B., and Castle, W. B.: *Ibid.*, 185, 539, 1933. (8.) Strauss, M. B., and McDonald, W. J.: *J. Am. Med. Assn.*, 100, 1320, 1933.

A HUMAN GALL STONE COMPOSED OF CALCIUM PALMITATE.

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THE gall stone which will be described was essentially a calcium soap, a type extremely rare. We could only find 3 other such cases in the literature; that most similar dates back to 1847. A complete

examination of the many papers dealing with biliary calculi might reveal a few more like cases; unfortunately the titles of such papers seldom give a clue to the composition of rare stones, even when hinting at unusual nature.

Case History. J. M., male, aged 64, was admitted to the Winnipeg General Hospital on February 6 last, complaining of general malaise, and of having been ill for the previous 18 months. He was senile and non-coöperative, no accurate information of his previous illness could be obtained, and no definite symptoms were apparent. He was placed on a light diet, without other treatment, and kept under observation. His temperature and pulse were normal until February 19, when the former rose to 102° F. (subsiding next day), but his pulse increased and remained above normal. There were still no other definite symptoms. He died on the 21st, of lobar pneumonia.

At *autopsy* (Dr. Sara Meltzer, Assistant Pathologist) the only pathologic findings, other than presence of empyema and a pleural exudate, were associated with the liver and the gall bladder. The liver weighed 1800 gm., and was smooth and dark red in color. The cut surface showed yellowish areas and was softer than normal. Microscopically, there was some slight fatty degeneration. "The gall bladder is large and pale, and contains thin yellow bile. There is also a single calculus of very unusual appearance. It is elongated, 3.5 cm. in length, and 1 cm. in diameter. The surface is yellow. On section it shows a small dark mixed nucleus, but the greater part of the calculus is yellow, firm, and homogeneous." The stone was lying free in the gall bladder, and there was no evidence of any occlusion of the duct. Microscopic examination of the gall bladder showed no inflammatory change.

Dr. Meltzer was kind enough to give the stone to one of us for chemical examination.

Examination of the Gall Stone. The stone, as received in two pieces, weighed 2.25 gm. The material was somewhat friable, with a soapy feel; there was a suggestion of concentric structure. The stone was of canary-yellow color throughout, except for a small brownish-black portion near the center.

The yellow material appeared to be practically insoluble in water, alcohol, acetone, chloroform, and benzene, and in hot dilute sodium hydroxide. After treatment with chloroform, the solvent gave a negative Salkowski and a doubtful Liebermann reaction for cholesterol. The material (0.1 gm.) was thoroughly extracted with ether and the ether evaporated; an unweighable trace of solid remained, which was extracted with chloroform. The extract gave with the Liebermann test a purple color, changing to bluish. This result seems to exclude cholesterol, and suggests that a trace of a cholic acid or similar compound was present.

None of the lipid solvents extracted the yellow color.

A trace of the original material was heated in a nickel spoon; it burned with a smoky flame, and left a white ash. The flame test showed the presence of calcium, but indicated that not more than the faintest trace of sodium was present. The 2,4 dinitrophenol "spot" test for potassium³ was negative.

The yellow material dissolved readily in cold glacial acetic acid, and addition of water to the solution threw down a heavy precipitate which retained the yellow color. When the precipitate was boiled with dilute acetic acid, and then cooled, pure white crystals separated. The yellow supernatant acid fluid changed slowly in color on standing to a definite green, indicating that the original color was due to calcium bilirubin, and

that the freed bilirubin had slowly changed in solution to biliverdin. The white crystals were easily soluble in chloroform and other lipoid solvents.

The behavior of the yellow material strongly suggested that it consisted of a calcium compound of one or more fatty acids. Accordingly the crystals thrown down from acetic acid were recrystallized from aqueous alcohol, and their melting point determined to be 62 to 63° C. Palmitic acid melts at 62.6° and stearic acid at 69.3° C. On account of Thudichum's results, referred to later, indicating that a melting point of the order found might be due to stearic acid contaminated with a trace of oleic acid, removable from it with difficulty, the recrystallized material was further twice recrystallized from aqueous alcohol. The product still showed the same melting point. It was then fractionated from aqueous alcohol, but the first fraction (which should contain any stearic acid) showed the identical melting point. Finally, since Scheringa¹⁰ has shown that potassium palmitate is ten times more soluble in 49% alcohol than is potassium stearate, this therefore affording a good method of separating these acids, the purified acid was dissolved in absolute alcohol and potassium ethylate added, the precipitated potassium soap was filtered and dried, and then dissolved in 49% alcohol, in which it was found to be very soluble. The solution was acidified and water added, reprecipitating the original acid, which was once more recrystallized from aqueous alcohol; the product gave the melting point 62 to 63° C. (corr.). A mixture of this product with purified palmitic acid of correct melting point gave exactly the same figure. Hence we conclude that the acid obtained from the stone was pure palmitic acid, and that stearic acid was absent. The iodine number was zero, supporting the conclusion that oleic acid was also absent.

These conclusions were confirmed by estimations of the acid value by titration with N/50 alcoholic sodium hydroxide. These were carried out with pure palmitic and stearic acids, and with the original recrystallized acid, before preparation of the potassium salt. Fifty or 60 mg. were used for each titration, and the results have been calculated to 100 mg. for comparison. Duplicate determinations were made in each case.

Pure stearic acid required	(i) 17.63 cc.	Mean, 17.66 cc.
	(ii) 17.68 cc.	Theory, 17.61 cc.
Pure palmitic acid required	(i) 19.42 cc.	Mean, 19.49 cc.
	(ii) 19.56 cc.	Theory, 19.53 cc.
The unknown acid required	(i) 19.37 cc.	
	(ii) 19.61 cc.	Mean, 19.49 cc.

Part of the stone (0.5040 gm.), containing an approximately proper proportion of the dark center, was dissolved in glacial acetic acid, and centrifuged to remove some brownish-black insoluble material, which, after drying, amounted to 0.0245 gm. (4.86%). The solution, with washings from the insoluble portion, was diluted with water until no further precipitate was thrown down. The yellow precipitate was filtered off, washed, and dried to constant weight at 37° C. It weighed 0.4045 gm. (80.3%). By virtue of the exact examination already described, this precipitate was considered to consist of palmitic acid, colored by a trace of bilirubin. A portion (49.5 mg.) was dissolved in 10 cc. of chloroform, and compared in a colorimeter with 0.16 mg. of pure bilirubin also dissolved in 10 cc. of chloroform. The colors matched perfectly, and the comparison indicated the presence of 0.18 mg. of bilirubin in the quantity assayed, representing 0.36% of the original material; the true figure for palmitic acid was therefore 79.9%.

The filtrate from the palmitic acid was evaporated to dryness, the residue dissolved in dilute hydrochloric acid, neutralized with sodium hydroxide, and made up to known volume. Calcium was estimated by Clark and

Collip's method,² which gave the figure 43.7 mg. for the total solution, corresponding to 8.7% of the original material.

Some (0.1425 gm.) of the original material was ignited to constant weight. The ash weighed 0.0220 gm. (15.4%). It was dissolved in dilute hydrochloric acid and made up to known volume. Phosphate was estimated in the solution by the method of Benedict and Theis,¹ and amounted to 0.0055 gm. as PO_4 , calculated to the total quantity taken (3.9%). The solution also contained magnesium, but in unestimable amount; the ammonium thiocyanate test showed presence of a trace of iron.

The brownish-black material insoluble in glacial acetic acid was examined separately. When a trace of it was warmed with 10% sodium hydroxide, a small proportion dissolved to a green solution. This was thought to be adherent biliverdin. The bulk of the material did not dissolve. This residue gave a negative Gmelin's test for bile pigment, although it slowly dissolved in strong nitric acid, apparently through oxidation. It was considered to be the ill-defined ultimate oxidation product of bilirubin usually termed "bilihumin."

Some of the brownish-black material (8.3 mg.) was strongly ignited to constant weight; 1.5 mg. of gray ash was left, which contained calcium, phosphate, and a trace of magnesium (detected by the Titan-yellow test⁶). This mineral matter is, at least in part, already included in the estimations of phosphate, and, correcting for it, the bilihumin content of the original material is approximately 4.0%.

Some of the original material (82.3 mg.), heated to 105° C. to constant weight, lost 2.2 mg. of water, 2.7%.

Conclusions from the Analyses. Since 79.9% of palmitic acid was found, this required 6.2% of calcium for complete combination. The phosphate (PO_4), 3.9%, required 2.5% of calcium for combination as $\text{Ca}_3(\text{PO}_4)_2$. The total calcium required, therefore, agreed with the 8.7% found (but the brownish-black material also contained a trace, which was not estimated). It can be concluded with reasonable certainty that calcium palmitate and tribasic calcium phosphate account for practically all the palmitic acid, phosphate, and calcium found.

The ash, 15.4%, can be similarly accounted for. The calcium oxide corresponding to 79.9% of palmitic acid equals 8.7%, which, added to 6.4% calcium phosphate, gives a total of 15.1%. Other mineral constituents could only be present in traces.

Hence the composition of the calculus can be stated fairly accurately as:

Calcium palmitate	85.8%
Calcium phosphate	6.4%
Calcium bilirubin	0.4%
"Bilihumin"	4.0%
Iron, magnesium	Traces
A cholic acid (?)	Trace
Water	2.7%
Unaccounted for	0.7%
	<hr/>
	100.0%

Roentgen Ray Examination. A Roentgen ray photograph* of somewhat less than half the stone, taken through 8 inches of paraffin

* We are indebted to Dr. H. M. Edmison, Assistant Radiologist to the Winnipeg General Hospital, for this photograph.

wax, showed a distinct and fairly even opacity, indicating an even distribution of calcium salts throughout the stone, and probably indicating that such a stone could be detected during life.

Discussion. Frerichs⁴ in 1847 found that a human gall stone from the museum at Gottingen contained 68% calcium palmitate and 28% cholesterol. Fatty acid crystals prepared from the stone melted at 58° C., which suggest that they were not pure palmitic acid. Thudichum (1863)¹¹ analyzed a gall stone from John Hunter's collection. It yielded fatty acid crystals which melted at 60° C., but repeated recrystallization from hot alcohol gave a fraction melting at 71° C. His analysis indicates that the stone contained 84% of calcium stearate (including a trace of oleate); cholesterol was absent. Fouquet (1896)³ analyzed a gall stone consisting largely of calcium stearate and phosphate, with but a trace of cholesterol. Identification of fatty acid crystals prepared from the stone seems to have been based on a melting point of 70° C. and the crystal form. He was unaware of the earlier reports.

Thudichum refers to presence of traces of calcium soaps in ordinary gall stones. Salkowski⁹ found traces of fatty acids (chiefly palmitic acid) in mixed cholesterol and pigment stones, with less calcium than corresponded to them. He made no reference to the above reports. Classifications of biliary calculi, subsequent to that of Thudichum, do not list calcium soap stones.

The present report seems to be the first of this type associated with a case history, and, unfortunately, that history gives no clue to the mechanism of formation of the stone. Little can serviceably be said on this point. Passage of soluble soaps from intestine to gall bladder should lead to a mixed calcium soap, were this formed, instead of the calcium palmitate here reported; such passage is in any event extremely improbable.

Bile usually contains traces of soluble soaps, and of calcium.^{5,7} Calcium soap stones are probably formed from biles containing such constituents in unusual proportions, and illustrate a rare type of aberrant metabolism. To theorize further seems unprofitable at present.

REFERENCES.

- (1.) Benedict, S. R., and Theis, R.: *J. Biol. Chem.*, 61, 63, 1924. (2.) Clark, E. P., and Collip, J. B.: *Ibid.*, 63, 461, 1925. (3.) Fouquet, L.: *J. de pharm. et chim.*, (vi), 3, 117, 1896. (4.) Frerichs, F. T.: *Diseases of the Liver*, vol. II, New Sydenham Society, London, 1861, quoted by Thudichum (Ref. 11). (5.) Hawk, P. B., and Bergeim, O.: *Practical Physiological Chemistry*, 10th Ed., Chap. XVIII, Philadelphia, P. Blakiston's Son & Co., 1931. (6.) Kolthoff, I. M.: *Chem. Weekblad*, 24, 254, 1927. (7.) Mathews, A. P.: *Physiological Chemistry*, 5th Ed., p. 446, New York, William Wood & Co., 1930. (8.) Rosenthaler, L.: *Microchem.*, 2, 29, 1924. (9.) Salkowski, E.: *Ztschr. physiol. Chem.*, 98, 25, 1916-17. (10.) Scheringa, K.: *Chem. Weekblad*, 29, 605, 1932 (*Abstr. in Chem. Abst.*, 27, 677, 1933). (11.) Thudichum, J. L. W.: *Treatise on Gall-stones*, London, John Churchill & Sons, 1863.

END-RESULTS FOLLOWING CHOLECYSTECTOMY.

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To the many analyses of the results following upon cholecystectomies, we are adding ours in the hope that out of these studies there may arise better criteria for determining what types of patients will secure sufficient relief from the operation to justify the measure. At present, despite careful study of each patient who comes under our care, and despite judicious selection of the patients with cholecystitis or cholelithiasis or both, we find a disappointingly large group who have little or no relief from the symptoms for which the cholecystectomy was performed.

From January 1, 1930, to December 31, 1934, there were 239 cholecystectomies performed on the charity division of this hospital, omitting all private patients. Of this number, 33 had some type of common duct operation at the same time. Furthermore, during this period there were many cholecystotomies, explorations of the gall bladder and biliary tract operations which are not included, because we have limited this study to the effect of cholecystectomy for benign lesions.

Ten of the patients died, making a mortality of 4.2% for the whole series. Of the 33 patients with common duct drainage, 4 died: a mortality for this subgroup of 12.1%. One of these deaths was probably due to coronary occlusion. Of the 206 patients with simple cholecystectomy, 6 died: a mortality of 2.9% for this subgroup. These deaths included 3 patients: 1 of 55 years who had a coronary occlusion with sudden death a few hours after operation; 1 of 58 years who came in with hypertension and decompensation and jaundice and died of pneumonia; a third patient of 65 with diabetes and chronic myocarditis who developed a thrombophlebitis of the right leg 10 days postoperatively and finally died of pneumonia. This leaves 3 cases (1.5%) who may be considered as straight operative deaths. In a larger group of 1624 patients with gall-bladder operations of all types, and including private and charity patients, there were 68 deaths, or again 4.2% mortality.

Of the 239 patients, 208 were females and 31 were males. The ages ranged from 16 to 70 years with 76 (32%) between the ages of 31 and 40, and 74 (31%) between the ages of 41 and 50; in other words, about two-thirds of the patients were in the fourth and fifth decades (Table 1).

TABLE 1.—AGE INCIDENCE.

	Male.	Female.
11-20	6
21-30	45	39
31-40	8	68
41-50	10	64
51-60	7	24
61-70	1	6
Unknown	1
Total	31	208

Symptoms. One hundred and sixty-eight patients had demonstrable gall stones. In this series the predominant symptom was pain in the right upper quadrant and epigastrium; this occurred in 163 cases (97%). In the great majority there was a history of radiation of the pain. Nausea was the second most common symptoms occurring in 132 patients (79%). Vomiting occurred in 62% of the cases; belching in 53%. Food idiosyncrasy was a definite complaint in somewhat less than half of the cases. Bloating occurred in a third, and jaundice was present in 46 (27%). Heartburn was complained of in a fifth of the cases. Fevers and chills and clay-colored stools were present in approximately 1 out of 10 cases (Table 2).

TABLE 2.—INCIDENCE OF SYMPTOMS.

Symptom.	Cases with stones. Per cent.	Cases without stones. Per cent.
R.U.Q. } pain	163 (97.0)	66 (93.0)
Epigastrie }		
Radiation of pain	121 (72.0)	42 (59.2)
Bloating	57 (33.9)	29 (40.8)
Belching	89 (53.0)	36 (50.7)
Heart burn	34 (20.2)	15 (21.1)
Nausea	132 (78.6)	56 (18.9)
Vomiting	104 (61.9)	39 (54.9)
Food idiosyncrasy	70 (41.7)	30 (42.3)
Fever and chills	22 (13.1)	7 (9.9)
Constipation	72 (42.9)	31 (43.7)
Melena	11 (65.0)	4 (5.6)
Clay stools	23 (13.7)	9 (12.7)
Jaundice	46 (27.4)	19 (26.8)
Headache	7 (4.2)	8 (11.2)

In 71 patients no stones were found at operation. In this series pain again was the predominating symptom, occurring in 93%, and here again the pain radiated in over half of the cases. Nausea was present in almost the exact proportion as in the group with stones (80%). Vomiting was present in 55%; belching in 51%. Food idiosyncrasies were also found in a little less than half. Bloating was slightly more common than in the group with stones, being present in about 40%. Jaundice was present in 14 cases (27% of this series). Interestingly enough, jaundice is seen to be present to almost the same extent in those patients who had no stones in their gall bladders at the time of operation as in those who had

calculi. We cannot help but wonder whether, in those patients who had been jaundiced but in whom no stones were found, there had at some previous time been calculi which had made their way down the ducts and into the intestines; also, if these gall bladders were to be left *in situ*, would calculi again form? Heart burn, chills and fever, and clay-colored stools were as frequent in this group as in the group in whom stones were found at operation. None of these patients was jaundiced at time of operation and none has had jaundice since, so that we feel that in these cases we have not overlooked common duct stone (Table 2).

Results. In evaluating our results, we have omitted 55 patients whom we were not able to trace. From the remaining 184, we have subtracted the 10 deaths, leaving 174 patients followed for a period ranging from 1 to 6 years. Of these 174 who had cholecystectomies, 119 had stones and 55 had none.

In order to obtain some basis for the analysis, not only for ourselves but for the literature as well, we have divided the results into three distinct groups: 1, symptomatic cure; 2, symptomatic improvement; 3, no relief. By "symptomatic cure" we mean a complete subsidence of all the pre-operative symptoms which prompted cholecystectomy. By "symptomatic improvement" we mean relief of the major symptoms, a definite improvement in the well-being of the patient and a very definite affirmative response to the question "Do you think that the operation was worth while?" By "no relief" we mean that there was no outstanding subsidence of symptoms, and although occasionally the patients might affirm that the operation had been of help, yet they still suffered from the majority of their pre-operative complaints.

Study of Cases With Gall Stones. There were 119 cases of cholelithiasis, not counting the 7 who died in the hospital. Symptomatic cures were obtained in 66 (55%); symptomatic improvement in 32 (27%); and no relief in 21 (18%). In other words, only 82% of the patients were definitely improved by operation (Table 3).

TABLE 3.—RESULTS.

	With stones (126). Per cent.	Without stones (58). Per cent.
Sympt. cure	66 (55)	25 (45)
Sympt. improv.	32 (27)	12 (22)
No relief	21 (18)	18 (33)
Deaths	7	3

In comparing the results of the operation with the pathologic findings we noticed, strangely enough, that the percentage of good results increased with the severity of the lesions encountered in the gall bladder. From a pathologic point of view, the gall bladders in these patients were divided into five groups: 1, those with no demonstrable gross or microscopic lesion of the gall bladder wall; 2, those with fibrosis; 3, those with chronic cholecystitis; 4, those

with marked chronic cholecystitis; and 5, those with acute cholecystitis.* From a pathologic standpoint we might assume a progression of the disease from the first to the fourth of these categories.

Symptomatic cures were obtained in Group 2 (fibrosis) in 32% and symptomatic improvement in 41%, leaving no relief in 27% of the patients. In Group 3 (chronic cholecystitis) symptomatic cure was obtained in 58%, symptomatic improvement in 28%, and no relief in 14%. In Group 4 (marked chronic cholecystitis) presumably the group in which the disease had lasted the longest or had made the severest inroads, symptomatic cure was obtained in 67%, symptomatic improvement in 13%, and no relief in 20%. In other words, the patients falling into Group 4 had a symptomatic cure twice as often as those in Group 2 (Table 4).

TABLE 4.—LESIONS FOUND IN THE GALL BLADDER.

<i>With Stone.</i>				
	Cure. Per cent.	Improv. Per cent.	No relief. Per cent.	Death
No chge.	4			
Fibrosis	7 (32)	9 (41)	6 (27)	1
Chr. cholec.	44 (58)	21 (28)	11 (14)	5
Marked chr. cholec. . . .	10 (67)	2 (13)	3 (20)	1
Ac. cfolec.	1		1	
<i>Without Stone.</i>				
No chge.	1 (25)	2 (50)	1 (25)	
Fibrosis	12 (48)	5 (20)	8 (32)	
Chr. cholec.	8 (38)	5 (24)	8 (38)	1
Marked chr. cholec. . . .	4 (80)		1 (20)	2

In an endeavor to see if there were any correlation between the length of duration of the symptoms and the degree of the lesion, we tabulated our cases with this in mind. Interestingly enough, the various histopathologic divisions had about the same relative number of cases, irrespective of whether the symptoms were of less than 1 year's duration, from 1 to 2 years, from 2 to 3, from 3 to 5, or from 5 to 10 years. In the group complaining of symptoms for more than 10 years, we find a very slightly elevated number in the marked chronic cholecystitis group.

The duration of the symptoms varied greatly, from a few months to many, many years. It would seem likely that the shorter the duration of the symptoms the greater the percentage of benefits; this was only partially borne out by our findings, namely, that in patients with symptoms for less than 2 years, 87% had symptomatic cure or improvement and only 13% had no relief; with symptoms of from 2 to 5 years' duration, 80% were cured or improved and 20% had no relief; with symptoms of from 5 to 10 years, 96% were cured or improved, and 4% had no relief; but when symptoms had been present for over 10 years only 58% were cured or improved

* There were 2 patients in this group with microscopic findings of an acute lesion, although clinically both patients were considered non-acute.

and 42% had no relief. It seemed peculiar to us that the group having symptoms for a period of 5 to 10 years should have shown better results than those having symptoms for a shorter period. However, this correlates with our observation that symptomatic cure was commonest where change was severest, that is, in those patients whose gall bladders showed marked chronic cholecystitis.

When we check our results against the age of the patients, we find the poorest results in the age groups of 11 to 20 and 51 to 70 years; the best results between the ages of 21 and 40 years, with nearly as good results between the ages of 41 and 50 (Table 5).

TABLE 5.—RESULTS BY AGE INCIDENCE.

	<i>With Stones.</i>			
	Cure. Per cent.	Improv. Per cent.	No relief. Per cent.	Death.
Unknown		1		
11-20	1 (25)	2 (50)	1 (25)	
21-30	11 (58)	6 (32)	2 (10)	1
31-40	17 (53)	12 (38)	3 (9)	1
41-50	28 (62)	9 (20)	8 (18)	1
51-60	9 (53)	2 (12)	6 (35)	2
61-70			1	2
	66	32	21	

Thirteen patients had had a cholecystostomy at some previous date; of these, 4 had relief for less than 1 year, 4 from 1 to 5 years, 2 were relieved for a period of 6 or 7 years, and 3 for over 10 years.

Of the patients, 33 had a drain inserted into the common duct in addition to the cholecystectomy. The common duct was drained either because stones were palpable in the duct, or because the duct was greatly distended, or because of jaundice either before or at the time of operation, leading us to suspect a stone. Three of these were patients in whom no stone could be found either in the gall bladder or in the common duct. One of these died as a result of periportal infection. The other 2 had symptomatic cures. Of the 30 patients with cholelithiasis who had common duct drainage, 3 died; 15 had symptomatic cures, 6 had symptomatic improvement; or, in other words, 78% had cure or improvement and 22% had no relief. If one combines the non-calculous and the calculous group with common duct drainage, we find that there were 4 deaths, that is 12% of the cases of common duct drainage. We do not have a large enough series of cases with common duct drainage to draw conclusions of any real worth; but we would like to point out that the mortality rate is 4 times as high as in simple cholecystectomy.

Non-calculous Cases. For many years we have felt that our results after cholecystectomy in patients without gall stones have been poor. For this reason we have refrained from operating unless there has been definite evidence of stones either by Roentgen ray or from a history of repeated gall-bladder colic. Therefore, nearly

all the cholecystectomies reported in this group had so-called typical symptoms (Table 2).

There were 58 patients (including 3 who died postoperatively) who had no gall stones either in the gall bladder or ducts whom we have followed for at least a year since they had a cholecystectomy. Of those living, 25 had symptomatic cure and 12 had symptomatic improved (67% cured or improved), while 33% had no relief. It is interesting to compare these figures with those of the group with calculi, where 82% were cured and improved and only 18% had no relief. We think that small as this group may be and in view of the careful selection of cases for operation, that this is a very significant difference (Table 3).

Studying this group of non-calculous cholecystectomies, from a histopathologic point of view, we find marked gall-bladder changes which may or may not account for the symptoms. Fibrosis was present in almost half of the cases, chronic cholecystitis in about 40% and marked chronic cholecystitis in about 9%. These findings support our previous contention that many of these gall bladders may have contained stones at some earlier date. As in the group with stones, the best results were obtained in those cases showing marked chronic cholecystitis.

Regarding any correlation between the length of duration of symptoms and the degree of damage present, we can only say that we were unable to discover any.

The duration of symptoms seemed to effect the results somewhat, namely, that in this group the better results were obtained in those having had symptoms for less than 5 years, 75% cured or improved; and 50% cured and improved in those having had symptoms for more than 5 years.

When we compare our results to age incidence, we find that regardless of the decade about a third of the patients had no relief.

Four of the patients in this group had had a cholecystostomy at some previous time; 2 had had relief for less than 1 year, 1 had relief for 4 or 5 years, and 1 for 6 or 7 years.

Summary and Conclusions. 1. Of 239 patients with cholecystectomies performed from 1930 to 1935 on the charity service, 31 were men and 208 women; about 63% were between 31 and 50 years.

2. Epigastric and right upper quadrant pain was the most common symptom in both calculous and non-calculous types of cases.

3. Seventeen patients had previous cholecystostomies, of whom 8 had relief for less than 3 years.

4. There were 10 deaths, or 4.2% of the cases in the entire series, including all types of complications. Of these 33 cases with common duct drainage in addition to the cholecystectomy, the mortality rate was 12.1%, leaving a mortality of 2.9% for all cases in which cholecystectomy alone was done. This figure includes all

cases irrespective of age, acuteness of gall-bladder lesion, cardiac failure or other unforeseen postoperative events.

5. Of 119 patients with calculous gall bladders who had been followed more than 1 year, 55% had symptomatic cure; 27% had symptomatic improvement and 18% had no relief, or 82% cured or improved by operation.

6. Of the patients with non-calculous gall bladders, 58 were studied: 45% had symptomatic cure, 22% symptomatic improvement, and 33% had no relief.

7. It seems that the best results are obtained in those cases where stones are present. Furthermore, that the more definite the symptoms the more apt there is to be complete recovery from operation.

8. Searching the literature we find a great variance in reports and a surprising inconsistency in the percentage of cures. One thing, however, appears certain, and that is that all is not as it should be in gall-bladder surgery.

9. We believe that continued and careful studies of large series of patients who have been operated upon for benign disease of the biliary tract will aid in establishing better standards by which to select those patients in whom results will justify the risks of operation.

BUNDLE BRANCH BLOCK WITH SHORT P-R INTERVAL IN INDIVIDUALS WITHOUT ORGANIC HEART DISEASE.

CASE REPORT WITH REVIEW OF LITERATURE.

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THE peculiar syndrome called bundle branch block with short P-R interval in individuals without organic heart disease has aroused great recent interest. A late experience with this condition has led to a review of the literature and a report of a case. Although it is true that the number of reported cases is small—to date only 45—it seems apparent from the rate with which reports are now appearing that this condition will soon be recognized as not infrequent. Aside from the increase in general interest this is one of the gratifying disorders encountered in medicine, gratifying because the diagnosis can be made with absolute certainty with the aid of the electrocardiogram, and once made, one can give the patient and his family complete assurance that his disorder will not shorten his life nor restrict his activity in any way.

Review of Literature. The first reported case, a man, aged 23, with attacks of paroxysmal tachycardia for 11 years, was described and carefully reported by Wilson¹³ in 1915. Wedd¹² reported the

next case in 1921, and Hamburger⁴ in 1929, but not until a year later when Wolff, Parkinson, and White¹⁵ collected and reported 11 cases, with careful follow-ups to 4 years, did the phenomenon become a clinical entity. The work of these three men soon stimulated interest in cardiologic circles all over the world, with the result that there has been a steady increase in the number of recorded cases since 1930. To wit: Pezzi⁷ reported 3 cases in 1931, Holzmänn and Scherf⁵ 2 in 1932. Wolferth and Wood¹⁴ reported 9, and Sigler⁹ 1 in 1933.

In the past year there have been several single and multiple case reports from various parts of the world. Roberts and Abramson⁸ reported 1 case. Sprague¹⁰ recently added a case associated with paroxysms of auricular fibrillation without any other evidence of organic heart disease. Faxen³ reports from Sweden an example in a boy of 11. From Peiping, Tung¹¹ reports 2 cases in detail, and mentions 3 others.

The most enlightening of last year's communications came from the Argentine, where Cossio, Berconsky and Kreutzer² reviewed 27 cases from the literature, added 7 of their own, and analyzed the group statistically from the standpoint of age, sex, type of tachycardia, presence or absence of coincidental organic heart disease and remission to a normal electrocardiographic configuration.

Case Report. Two years ago an opportunity was offered to observe an example of this condition. The patient was the only son of a Spanish family living in Mexico, referred by their doctor for an opinion and advice regarding a strange myocardial disorder. Attention had been directed to his heart because of a short attack of paroxysmal tachycardia which had occurred while climbing a mountain. Medical advice was sought immediately, but on physical examination no abnormal findings were disclosed, and the patient and family were reassured. Three months later there was a second attack while descending a flight of stairs. This was associated with slight palpitation, dryness of the mouth, headache and a pulse rate of 220. Again the duration of the attack was short. An electrocardiogram taken after the attack showed a widened *QRS*, and a notching of the *R* waves, suggestive of an incomplete bundle branch block, and in addition an abnormally short *P-R* interval. Search for an etiologic factor disclosed a faintly positive blood Wassermann reaction, and though the Wassermann of both parents was negative, the patient was given a series of 12 intramuscular injections of colloidal bismuth. The boy was taken out of school and kept under strict medical supervision for 7 months. During this time four electrocardiograms were taken, no two of which were exactly alike, but all four consistently showed a short *P-R* interval, a widened *QRS*, and slurring of the *R* wave. There were no more attacks and at no time was there any evidence of cardiac insufficiency.

His history revealed nothing suggestive of a familial disorder; there are 2 younger sisters who are perfectly well. His health was first interrupted at the age of 4 by a disorder of the lower bowel which was said to be colitis; this cleared up in 3 months and has not recurred. At 5 he had measles, followed by whooping cough; 6 months later he had a series of attacks of fever and headache, with normal health between. Following some sort of vaccine therapy the attacks disappeared and have never recurred. For the remainder of his childhood and early puberty he enjoyed good health and a normal

school life. He has never had scarlet fever, diphtheria, tonsillitis, or any rheumatic manifestations.

His family brought him to New York in December, 1936, after spending a harrowing 7 months closely guarding his health and activity and being constantly fearful of the outcome of his disorder.

On physical examination he appeared to be a tall, thin, somewhat lethargic boy of 14 who looked perfectly well. The blood pressure was a little below the usual level—100/60, but the remainder of the physical examination was entirely negative.

Laboratory findings disclosed a 3+ albumin in his urine, with rare hyaline and granular casts on centrifuged specimen. This finding was at first disturbing, but repeated specimens obtained before getting up in the morning were entirely clear, while those after standing showed albuminuria. It was concluded that his albuminuria and microscopic findings were on a functional orthostatic basis. Complete blood count, erythrocyte sedimentation rate, blood non-protein nitrogen and blood sugar were all within normal limits. Basal metabolic rate was -21 , which may have accounted for his apparent lethargy. Wassermann and Kahn tests, done by different laboratories, were negative.

Electrocardiograms showed the same abnormal graph, previously observed in Mexico, namely a short $P-R$ interval, a widened QRS and slurring of the upstroke of the R wave (Fig. 1). As the clinical and electrocardiographic findings seemed identical with the cases described by Wolff, Parkinson and White,¹⁵ and as the abnormal graph could be abolished in their cases by the use of atropine or exercise, an attempt was made to determine whether this patient might also respond electrocardiographically to these stimuli.

An electrocardiogram of Lead I (Fig. 2 B) was taken immediately after exercise (jumping up and down on one foot for 1 minute) and when compared with the control (Fig. 2 A) shows slight but definite changes. The $P-R$ interval is lengthened from 0.8 to 0.12 second; the QRS shortened from 0.1 second to 0.04. The thick slurring of the upstroke of the R wave is eliminated and the QRS takes on a normal configuration with slight increase in voltage. The change was so transient that it was lost in the change of Leads, so that in Lead II (Fig. 2 C) taken only a few seconds after Lead I (Fig. 2 B), there is a return to the original abnormality. Following the subcutaneous injection of 1/50 grain of atropine there was no change in the electrocardiogram; likewise no change was effected with 2 days of belladonna fluid extract 15 minims t.i.d. by mouth. Vagal pressure was attempted immediately after exercise and during the taking of an electrocardiographic tracing to determine whether the changes to normal following exercise could be prematurely reversed by this form of vagal stimulation. Exercise produced such a transient effect that it was impossible to determine in the vagus pressure experiments whether the change back to the old configuration was ever hastened by vagal stimulation. The diagnosis from any lished, the family could be assured that the boy was not suffering from any form of organic heart disease. Although he has not returned to New York, current communications with the family indicate that he has been living a normal life for his age in a preparatory school in Texas, and engaging in athletic activities, and has had no recurrences of his attacks of tachycardia.

Discussion. Comparison of this case with others, showed that the clinical and electrocardiographic features of this syndrome are clear cut—certainly well within the general variability of clinical syndromes. Usually occurring in young individuals of the athletic type, it is seen much more frequently in males than in females.

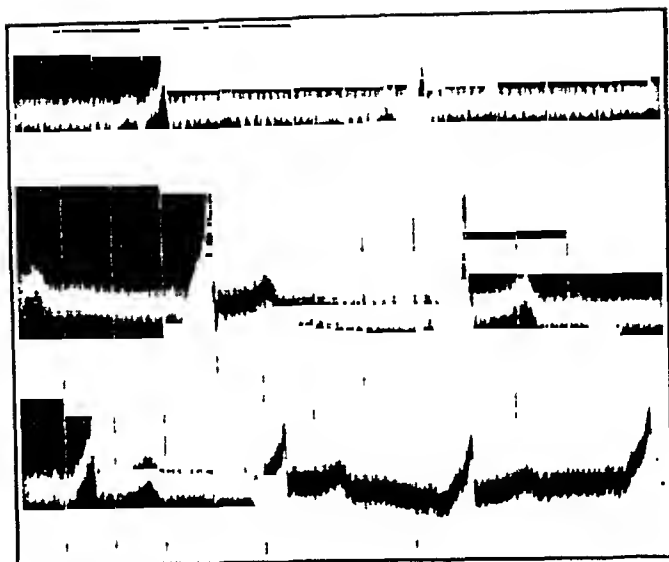


FIG. 1.—Electrocardiogram (5694), December 24, 1935. Intraventricular conduction defect with short *P-R* interval. *P-R*, 0.08 sec.; *QRS*, 0.1 sec.

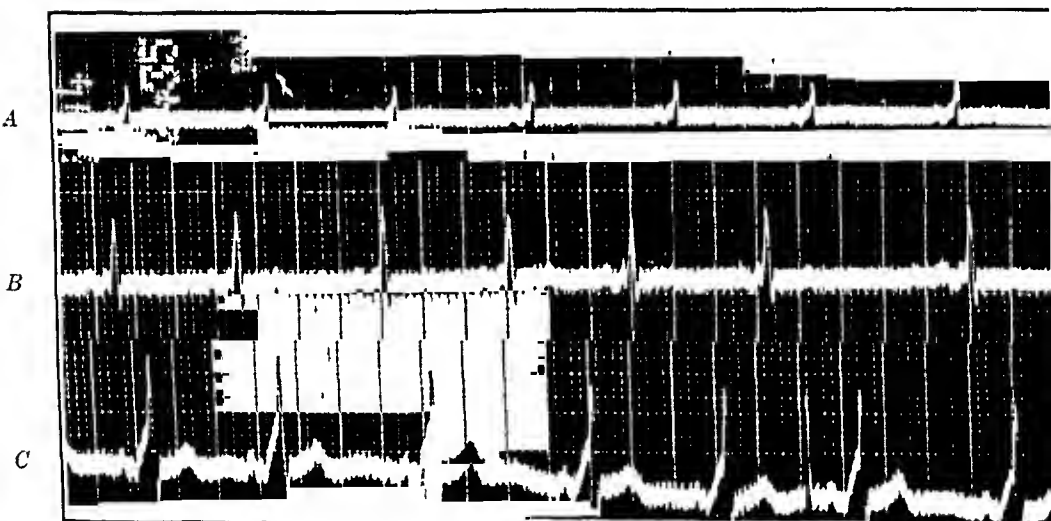


FIG. 2.—Electrocardiogram (5694), December 24, 1935. *A*, Lead I: control; *B*, Lead I: after exercise; *C*, Lead II: taken immediately after *B*.

It has been found in individuals in all age groups, from $4\frac{1}{2}$ to 62 years; but most frequently in the second, third and fourth decades, though the history usually dates back to puberty, or before, when the patient first began to experience periodic attacks of palpitation, sometimes induced by strenuous exercise, but almost as frequently occurring when the patient is at rest. There are, however, a few reported cases in which palpitation was never experienced. Whether or not these cases had tachycardia without palpitation, it is impossible to say. Wolferth and Wood¹⁴ reported 4 cases discovered accidentally during a routine study of normal electrocardiograms, or through electrocardiographic findings, as part of a routine examination. And Tung mentions 2 with characteristic electrocardiographic findings, who gave no history of palpitation and who had never been known to have tachycardia. In 1 case in the series reported by Wolff, Parkinson and White,¹⁵ the only cardiac symptoms were attacks of bradycardia associated with weakness and pallor. Although as a rule the presenting complaint is related to paroxysmal attacks of tachycardia, it becomes apparent that exceptions to this are not infrequent. This type of tachycardia, when present, is usually a simple paroxysmal auricular tachycardia. This was true in 39 of the 45 cases, while in the remaining 6 the tachycardia was on the basis of paroxysmal auricular fibrillation. (Wolff, Parkinson and White¹⁵ report 1, Wolferth and Wood¹⁴ 2, Cossio, Berkonsky and Kreutzer² 2, and Sprague¹⁰ 1.)

Although there are a few cases in which organic heart disease is present, the type of organic involvement is so diverse, including hypertension with acute glomerular nephritis, inactive rheumatic heart disease, and hypertensive cardiovascular disease, it is hardly conceivable that organic heart disease when encountered is more than coincidental.

Remissions to normal electrocardiographic configurations may occur spontaneously and may be experimentally induced. Electrocardiograms taken during the attacks of tachycardia are usually normal. Sometimes they are found to be normal without tachycardia and for no apparent reason. Whether these remissions are ever permanent or not it is difficult to say, as there are not to date sufficiently long-time follow-ups on these cases definitely to answer the question. The data on the effect of atropine and exercise are conflicting. It is interesting to note that in some cases these methods of vagus inhibition do abolish the electrocardiographic abnormality, but the significance of these selected observations belongs in the realm of pure speculation.

Although one may suspect the existence of this condition in a healthy young individual—usually a male with a history of paroxysmal tachycardia without clinical or roentgenographic evidence of heart disease—the key to the diagnosis is to be found in the electrocardiographic findings that show a short *P-R* interval, associated

with a widening of the *QRS* and abnormalities in the initial ventricular complex characteristic of an incomplete or complete intraventricular conduction defect. The most usual type is a left bundle branch block, with the initial ventricular complexes as seen in left axis deviation and the *T* waves in Leads I and III in the opposite direction from the main complex. There are several reported examples of right bundle branch block and of intermediate stages of incomplete intraventricular block, as it was in this case. If it were not for the presence of the short *P-R* interval (*i. e.*, 0.1 second or below), these electrocardiograms could not be distinguished from organic bundle branch block or from the so-called functional bundle branch block, as described by Cohn and Lewis,¹ Sigler,⁹ and others.

Views as to the etiology of this peculiar phenomenon are so diverse, experimental and clinical observations so contradictory, that it is impossible to reach any definite conclusions as yet. As there is no studied autopsy material available, it is conceivable that when obtained it may throw considerable light on the mechanism of the production of these electrocardiographic abnormalities. At present there is a sharp division between two schools of thought. One believes that it is a vagal effect induced by excess vagal tone which slows conduction through the bundle or one of its branches, relievable by suppression of the vagal influence by atropine or exercise. This was the view taken by Wolff, Parkinson and White,¹⁵ and Wedd¹² found that vagal inhibition brought about a transition of the electrocardiogram to normal. The second view is that of Wolfarth and Wood,¹⁴ Holzmann and Scherf,⁵ and Roberts and Abramson,⁸ who were unable to confirm these observations. In their cases the abnormal graphs were not affected by vagal inhibition. They postulate that some aberrant conduction bundle is present between the right auricle and right ventricle, such as the bundle of Kent,⁶ and that it is functionally able to transmit impulses. With this as a premise, they argue that the abnormal graph represents the passage of impulses through the pathway and that transition to the normal graph represents a return of the impulse to the normal pathway.

There are sufficient objections to both of these theories to make them untenable. With regard to the first theory, the following two facts have yet to be accounted for: (1) that there are many cases reported which show no effect from vagal inhibition; and (2) one case reported by Sigler⁹ which reverted to a normal graph after vagal stimulation.

Against the theory of an abnormal conduction bundle is the fact that such abnormalities have not yet been demonstrated.

With respect to prognosis, it is true that the follow-up studies in known cases have been to date too short to be conclusive. Yet it is the unanimous opinion of those who have studied this condition that the disorder is primarily functional, and the patient's progress unaffected by the electrocardiographic abnormality. This view is

supported by the character of the history and clinical picture, and several reported cases in individuals past middle life who continue to show no evidence of cardiac insufficiency. It so happens that the oldest reported case is only 62, but he is in perfect health.

Treatment. It might be said that these patients are suffering from an electrocardiogram and not a disease. Therefore, medicinal treatment assumes no importance, but psychotherapy and reassurance are paramount. As has been pointed out before, the individual or the family may have been told that the patient is suffering from a bizarre form of incurable heart disease, and in consequence suffered an untold amount of mental anguish over this thought.

Completely to destroy this concept may require psychotherapy to prevent the development of a cardiac neurosis in the patient, which might otherwise become a permanent handicap. In this particular case it was not an easy task; the family had spent 7 months reconciling themselves to the fate before them and were almost reluctant to relinquish the state of martyrdom to which they had become accustomed.

The individual should be encouraged to live a normal life, and if, as is frequently the case, he is of school age or college age, he should be allowed to engage in athletics, unless the attacks of tachycardia become sufficiently frequent to interfere. In the reported cases, as well as here, attacks have not infrequently followed severe exercise. Continued exercise, however, does not seem to increase the frequency of the attacks, for they may well occur at rest. Apparently a small percentage of individuals seem to outgrow their electrocardiographic difficulties, and this permanent change seems to have no relationship to the extent of their activities.

Summary and Conclusions. 1. A peculiar electrocardiographic phenomenon is described, associated with a short *P-R* interval, a widened *QRS* and slurring or notching of the *QRS*, characteristic of the so-called bundle branch block, except for the short *P-R* interval.

2. One case is reported and 44 cases collected from the literature.

3. The condition occurs usually in young individuals, prone to attacks of paroxysmal tachycardia, which is in rare instances on the basis of paroxysmal auricular fibrillation.

4. The etiology is entirely unknown.

5. In certain cases atropine and exercise will abolish the block temporarily, but there are too many examples which do not respond to these stimuli adequately to substantiate the theory that the phenomenon is entirely the result of excess vagal tone.

6. The diagnosis can be made by the electrocardiogram, for in no other condition is bundle branch block associated with a short *P-R* interval.

7. The disorder apparently has no pathologic significance, and does not in any way shorten the life span of the individual.

REFERENCES.

- (1.) Cohn, A. E., and Lewis, T.: *Proc. New York Path. Soc.*, 14, 207, 1914. (2.) Cossio, P., Berconsky, I., and Kreutzer, P.: *Rev. Argentine de Cardiol.*, 2, 411, 1936. (3.) Faxen, N.: *Aeta Paediat.*, 181, 49, 1936. (4.) Hamburger, W. W.: *Med. Clin. North America*, 13, 343, 1929. (5.) Holzmänn, M., and Scherf, D.: *Ztschr. f. Klin. Med.*, 121, 404, 1932. (6.) Kent, A. F.: *Brit. Med. J.*, 2, 105, 1914. (7.) Pezzi, C.: *Arch. d. Mal. du Cœur*, 24, 1, 1931. (8.) Roberts, G. H., and Abramson, D. L.: *Ann. Int. Med.*, 9, 983, 1936. (9.) Sigler, L. H.: *Am. J. Med. Sci.*, 185, 211, 1933. (10.) Sprague, H. S.: *Internat. Clin.*, 47th Ser., 1, 186, 1937. (11.) Tung, C. L.: *Am. Heart J.*, 11, 89, 1936. (N.B. 2 reported; 3 others mentioned.) (12.) Wedd, A. M.: *Arch. Int. Med.*, 27, 571, 1921. (13.) Wilson, F. N.: *Ibid.*, 16, 1008, 1915. (14.) Wolferth, C. C., and Wood, F. C.: *Am. Heart J.*, 8, 297, 1933. (15.) Wolff, L., Parkinson, J., and White, P. D.: *Ibid.*, 5, 685, 1930.

CRITERIA OF OXYGEN WANT, WITH ESPECIAL REFERENCE TO NEUROCIRCULATORY ASTHENIA.

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WE are accustomed to recognize anoxemia by the presence of symptoms. Particularly cyanosis has long directed attention to poor oxygenation of the blood. More recently (Waters¹⁰) much of the knowledge of symptoms of oxygen want has been organized so as to be of ready aid in diagnosis of anoxemia in cases where it is known to be a possible development, as in pneumonia, chest injuries, congestive heart failure, and so on.

However, objective criteria of oxygen want are too few, and if they could be worked out would help in the recognition of borderline anoxemia situations whose frequency and importance are now unknown.³

The best method for determining an oxygen lack due to faulty aeration of blood passing through the lungs is the analysis of arterial blood. This technique was introduced by Hürter.⁶ The application of analysis of arterial blood has been greatly facilitated by Van Slyke's development of his manometric gas analysis apparatus. Stadie,⁹ and others, with this apparatus have recorded low oxygen saturation results in pneumonia, heart disease, asthma and pulmonary fibrosis. Only a few normal subjects have been so studied,⁴ not enough to permit statistical determination of the normal, or a definition of a borderline range of saturation between clear-cut normals and clear-cut anoxemic individuals. The 16 normal sub-

jects we studied showed no evidence of any disorder of the cardio-respiratory mechanism. However, several came below the figure of 95% which is held to be "normal." In 16 normals so studied the arterial oxygen saturation ranged from 98.8 to 93.4%, with a mean of 95.6%. In 38 cases in the literature the range was from 93.2 to 100%, with a mean of 95.7%.

Since many conditions of anoxia are peripheral in type (*i. e.*, properly aerated arterial blood moves so slowly through the peripheral capillary bed that it is reduced in oxygen content below the optimum for tissue nutrition), the study of arterial blood should be supplemented by less direct methods which would show lack of adequate supply of oxygen to the tissues. Determination of venous lactic acid, together with a shift in this figure when oxygen is respired, might constitute evidence of oxygen want. The idea is based on observations of Hill,⁵ *in re* oxygen debt. We also attempted a second procedure aimed at detecting lack of oxygen on the following reasoning: If a patient is suffering from oxygen want, breathing oxygen instead of air should significantly alter the rate of oxygen consumption. Determination of tissue gas tension and of alveolar CO₂ was abandoned for various technical reasons as unsuited for this purpose.

Therefore, we adopted the plan of recording degree of oxygen saturation of arterial blood, along with venous lactic acid before and after breathing oxygen, and also determined the oxygen consumption of patients breathing air and breathing oxygen according to the following routine:

Methods. The brachial or femoral artery was punctured by passing a 20-gauge needle on a syringe containing novocaine through a novocaine wheal. This needle was slowly advanced, while novocaine was infiltrated, into the artery. Once the blood was flowing the syringe was changed for an oiled syringe containing a bit of powdered buffered oxalate and mercury (for mixing). Using an eccentric tip syringe it was easy to draw the blood without contact with air and store it in the syringe until ready for analysis. The oxygen content was regularly determined in duplicate on 2-cc. samples, using the manometric apparatus and standard technique.⁸ The oxygen capacity was similarly done after aerating a part of the same sample.

Oxygen consumption (breathing air and oxygen) was done as follows. The patient at basal conditions first had a basal rate taken by the Tissot tank method while breathing air. The samples were analyzed either by a Haldane or a Van Slyke apparatus by standard methods. After 5 to 8 minutes' rest this was repeated, using a Benedict-Roth machine rebreathing oxygen through soda lime. After another 3 to 5-minute interval the Tissot was repeated and finally the fourth determination of the morning was made by the Benedict-Roth apparatus.

The lactic acid determinations were made by the method of Friedman, Cotonio and Shafer.¹ The blood was drawn without stasis from the same cubital vein before and after rebreathing oxygen from a Benedict-Roth apparatus with the subject at basal conditions.

Results. The results of these 3 procedures on cases with clear-cut oxygen want are shown in Table 1. In cases having low arterial

oxygen saturation and hence an anoxemia the lactic acid shift was usually absent, even though a shift of 1 mg.% was considered significant. These low lactic acid figures are explained by the patients being at basal conditions. However the "basal by 2 methods" procedure shows one or the other or both Tissot results lower than the Benedict-Roth average results. Where the data are inconsistent, they are recorded \pm . The shift in the *R.Q.* was a rise of over 0.05 after breathing oxygen and could best be explained by the theory that an oxygen want was present, but was made good by breathing oxygen and afterward the oxygen "debt" reappeared when air was breathed. If there had been no interval this effect would result from the residual air in the lungs becoming almost pure oxygen and hence giving a low oxygen absorption and a high *R.Q.* in the second Tissot. The timing of the routine precluded this error.

TABLE 1.—RESULTS ON DECOMPENSATED ORGANIC HEART DISEASE.

Subject.	Arterial oxygen saturation (per cent).	Initial lactic acid.	Second lactic acid.	Shift.	Initial Tissot low.	Second Tissot low.	Shift in <i>R.Q.</i>
K.	82.0	7.4	5.9	Yes	\pm	\pm	\pm
D.	88.4	+	+	+
Go.	10.6	10.2	No	\pm	+	+
Ga.	94.0	\pm	+	+
U.	92.0	+	\pm	+
Wo.	96.4	{10.4 10.4}	{10.6 9.6}	No	+	+	+
Sc.	95.4	{7.4 9.4}	{6.7 9.2}	No	—	+	+
Wa.	93.8	+	\pm	+
St.	92.3	{10.7 13.3}	{9.6 11.4}	Yes	\pm	+	+
Wau.	92.0	7.5	8.9	No	—	+	+

The control group of healthy people are tabulated in Table 2. Where arterial puncture was not done there was no reason to suspect a low result.

TABLE 2.—NORMALS.

Subject.	Arterial oxygen saturation (per cent).	Initial lactic acid.	Second lactic acid.	Shift.	Initial Tissot low.	Second Tissot low.	Shift in <i>R.Q.</i>
B.	96.4	7.4	6.5	No	—	—	—
St.	94.0	—	—	—
Lo.	93.5	—	—	—
Sm.	—	—	—
Sl.	{7.0 8.1}	{7.2 7.4}	No	—	—	—
La.	8.5	8.0	No	—	—	—
Le.	9.0	8.3	No	—	—	—
G.	6.5	6.9	No	—	—	—

The striking results in a few neurocirculatory asthenia cases were not entirely foreseen. Table 3 lists the arterial oxygen saturation in several neurocirculatory asthenia cases who showed the symptoms described by Lewis⁷ and by White.¹¹ Undoubtedly in certain severe cases a true anoxemia exists. That in less severe cases an anoxemia

also is present is indicated by the results in Table 3 where again + signs predominate in the 3 columns to the right.

TABLE 3.—RESULTS ON NEUROSIS CASES.

Subject.	Arterial oxygen saturation (per cent).	Initial lactic acid.	Second lactic acid	Shift.	Initial Tissot low.	Second Tissot low.	Shift in R.Q.
C. . .	78 83 91	16.7 18.2	7.7 14.0	Yes	+	+	+
B. . .	83 86	16.2 6.5	13.5 5.2	Yes	=	+	+
F. . .	84	10.7 7.4	10.6 7.4	No	=	+	+
S. . .	85.6	+	+	+
W. . .	89.5	+	+	+
H. . .	92 93	13.7	8.0	Yes	=	=	=
	90 97	20.2 8.7 9.6	12.2 6.7 7.6				

In considering the reason for faulty aeration of blood passing through normal lungs we thought of possible "shunts" from pulmonary artery to vein, and shallow breathing, and marginal atelectasis. Greene² suggested that anoxemia could result with the chest in an expanded position, *i. e.*, an increased residual air, and a normal tidal air which would for that individual at the moment be an inadequate ventilation.

An interesting side issue was the observation that in any of these anoxemia situations elevated basal rates resulted on breathing oxygen, as though an oxygen debt were being made good. The clinical application of this fact must be of aid in the distinction of any anoxia from true elevations of B.M.R. This fact may help in the differential diagnosis of neurocirculatory asthenia and hyperthyroidism.

Summary. Neurocirculatory asthenia showed in 13 cases an inadequate arterialization of blood leaving the lungs. These patients also showed other indirect evidence of oxygen want in that the *R.Q.* and oxygen consumption altered with the patient breathing oxygen. These latter changes were regularly found in decompensated organic heart disease cases. Such findings support the opinion of Haldane that part of the symptoms of these patients are from anoxemia, especially the respiratory irregularities. These patients often present difficulty in differential diagnosis from hyperthyroidism, therefore a watch for evidence of oxygen want may bring certain B.M.R. results into suspicion of artificial elevation.

Conclusions. 1. The above criteria are definite evidence of oxygen want and together indicate whether it is pulmonary or peripheral in type.

2. Oxygen saturation of less than 94% appears insufficient optimally to supply the organism with oxygen, so that the "borderline" group having oxygen saturations of 90 to 94% are really in anoxia.

3. Neurocirculatory asthenia is featured by an oxygen want of pulmonary origin, present in certain patients. Anoxemia probably contributes to the fatigue of these patients and accounts for certain other symptoms.

4. An anoxic situation can give elevated basal metabolic rate results, if taken from oxygen-rebreathing apparatus.

REFERENCES.

- (1.) Friedman, T. E., Cotonio, M., and Shafer, P. A.: *J. Biol. Chem.*, 73, 338, 1927. (2.) Greene, J. A.: Personal communication, 1936. (3.) Haldane, J. S.: *Respiration*, New Haven, Yale University Press, 1927; Haldane, J. S., and Priestley, J. G.: *Respiration*, New Haven, Yale University Press, 1936. (4.) Harrop, G. A.: *J. Exp. Med.*, 30, 241, 1919; Meakins, J., and Davies, H. W.: *J. Path. and Bact.*, 23, 451, 1920; Himwich, H. E., and Barr, E. P.: *J. Biol. Chem.*, 57, 363, 1923; Barach, A. L., and Woodwell, M. N.: *Arch. Int. Med.*, 28, 367, 1921; Barcroft, J. et al.: *Phil. Trans. Roy. Soc., Sec. B*, 211, 351, 1923; Hurtado, A., Kaltreider, U. L., and McCann, W. S.: *J. Clin. Invest.*, 14, 94, 1935. (5.) Hill, A. V., and Lupton, H.: *Quart. J. Med.*, 16, 135, 1923. (6.) Hürter: *Deutsch. Arch. f. klin. Med.*, 108, 1, 1912. (7.) Lewis, T.: *The Soldiers' Heart and the Effort Syndrome*, New York, Paul B. Hoeber, Inc., 1919. (8.) Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry (Methods)*, Baltimore, The Williams & Wilkins Company, p. 324, 1932. (9.) Stadie, W. C.: *J. Exp. Med.*, 30, 215, 1919. (10.) Waters, R. M.: *Wisconsin Med. J.*, 31, 20, 1932. (11.) White, P. D.: *Heart Disease*, New York, The Macmillan Company, p. 429, 1931.

THE EFFECT OF LIVER EXTRACT ON THE ABSORPTION OF FAT IN SPRUE.

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A DISTURBANCE of the absorption of fat from the intestinal tracts of patients with sprue has been assumed to exist almost since the recognition of the disease. The belief in the existence of such a disorder of fat absorption has been based upon the presence of large amounts of fat in the feces of the patient with sprue during the acute phase of the disease and upon the absence of excess fat during clinical remissions.

Previous studies of the fat content of the feces of patients with sprue have indicated that it is largely split and that hence the disorder is not one of pancreatic function (Fairley²). It has not been clear, however, whether the diarrhea which is so frequently a symptom of sprue caused the malabsorption of fat or whether the presence of unabsorbed but split fat caused the diarrhea. No proof has been advanced furthermore that the fat in the intestine has not been absorbed and subsequently excreted.

Castle, Rhoads, Lawson, and Payne¹ described the improvement

of the intestinal symptoms of patients with sprue which follows the suitable administration of liver extract. Mackie, Miller, and Rhoads¹ demonstrated characteristic alterations of intestinal motility and outline by Roentgen ray examination, and Miller and Rhoads⁶ showed in one case that these alterations were less pronounced after liver extract had been injected and symptoms had disappeared.

This communication reports a study of the amount of fat which is present in the blood of normal subjects following the taking of a meal rich in fat, and compares the results with those in patients during exacerbations of the diarrhea of tropical sprue as well as during the remissions which follow the administration of liver extract.

Methods. The method employed for the determination of the blood lipids was that described by Kirk, Page and Van Slyke.³ Heparin was employed as an anticoagulant. The subjects fasted overnight and a sample of blood was taken before the test meal of fat. Samples of blood were withdrawn at 2, 4, and 6 hours after the ingestion of the fat. The meal was composed of heavy cream and butter in the ratio of roughly 6 to 1 with a small amount of bread as a vehicle for the butter. In the early experiments, the patients took 4 gm. of fat per kilo of body weight, but such a large amount of fat proved rather difficult to tolerate and in later studies the amount was reduced to 2 gm. per kilo. This decrease in the fat content of the meal seemed to occasion but slight variation in the results. Little discomfort resulted from the test, although in the subsequent 48 hours several bulky loose stools were frequently passed, particularly in cases during relapse. Diarrhea occurred in no case while absorption was being studied and when samples of blood were being withdrawn. The low concentration of fat could not be ascribed therefore simply to rapid loss of the administered fat from the intestinal tract. The time relationship between the intake of fat and defecation suggested strongly that malabsorption caused the abnormal stools rather than the reverse.

In the early experiments total lipid carbon, total lipid cholesterol, and lipid phosphorus were all determined. After repeated studies had shown that little or no change in the levels of free and of total lipid cholesterol occurred after the fat meal, these determinations were discontinued.

Results. As a preliminary study the amounts of lipid in the blood of 4 normal individuals before and after taking a fat meal were measured by the Kirk method. Previous studies on normal controls had employed techniques which differed from each other so considerably that the results are not comparable either with each other or with our findings.

The results are reasonably constant; Figures 1 and 2 and the fasting levels of total lipid carbon were uniformly in the range between 320 and 480 mg. %. The peak of the rise was reached at the end of 4 hours and the maximum level attained was between 550 and 650 mg. %. Free and total lipid cholesterol levels failed to show consistent changes, although they tended to rise slightly. Lipid phosphorus levels rose not more than 2 mg. % but were consistently increased. Following the maximum levels a gradual decrease tended to occur but in all instances the lipid content at the end of 6 hours was greater than the fasting level.

The results obtained from the study of the normal individuals were in agreement with those reported by Kirk, Page and Van Slyke on

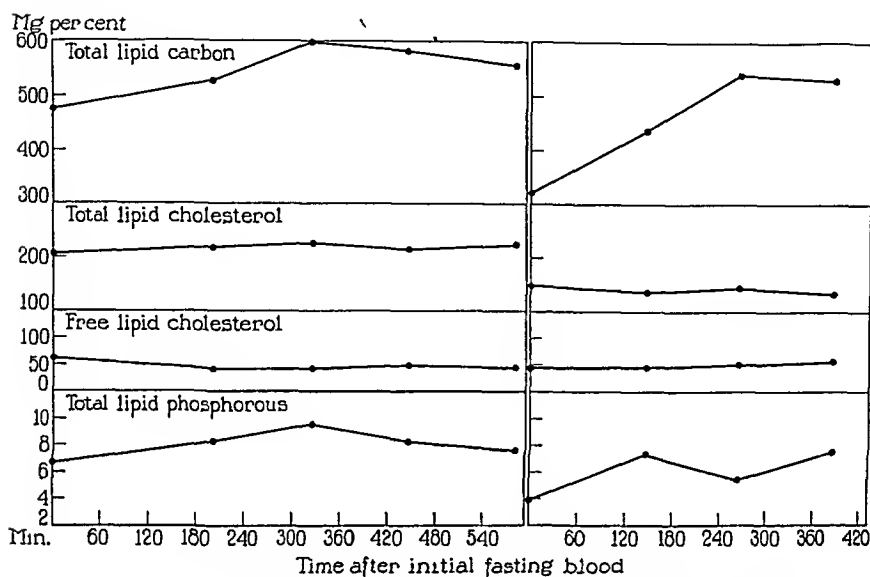


FIG. 1.—Blood-lipid patterns in 2 normal individuals following fat meal.

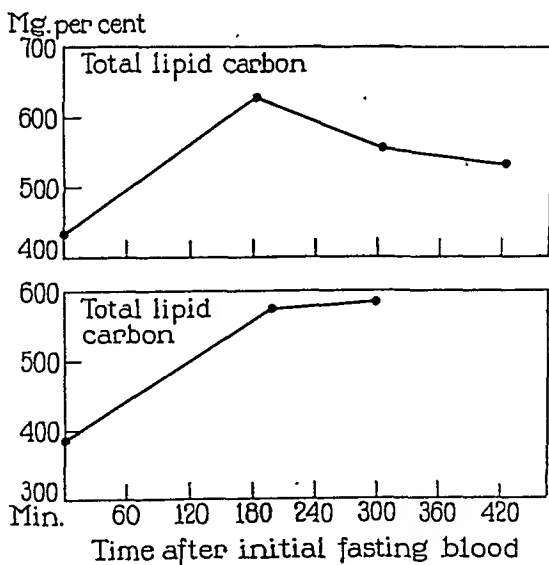


FIG. 2.—Total lipid-carbon curves of 2 normal individuals following fat meal.

fasting men and by Man and Gildea⁵ after a fat meal, although the latter workers employed a somewhat different analytical procedure.

After the amounts of lipid in the blood of normal subjects had been ascertained for the fasting state and after eating a meal of fat, 3 cases of sprue were studied before and after treatment with liver extract, and 2 more cases before but not after treatment. All 5 were cases of typical sprue, acquired in the tropics and of long duration. All had suffered from macrocytic anemia and stomatitis at

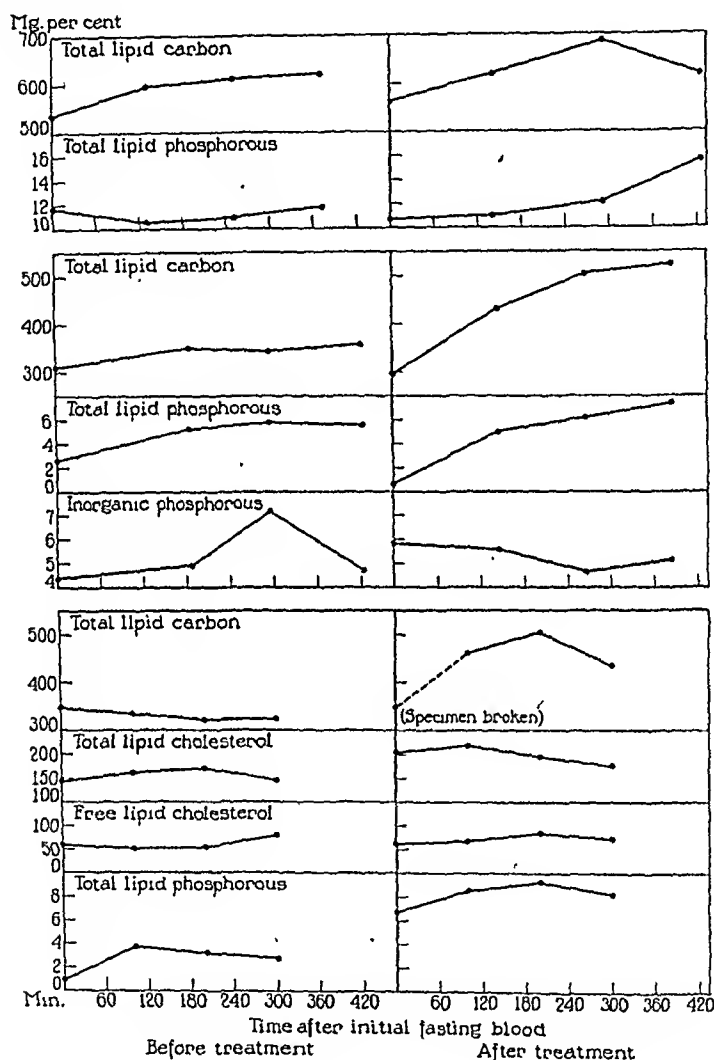


FIG. 3.—Blood-lipid patterns in 3 sprue patients following fat meal. On the left, the curves before liver-extract treatment; on the right, the curves following treatment.

one time, but when tested neither hematologic nor oral symptoms were prominent. Abdominal distention, gas, and bulky, soft, gray stools were distressing features and were characteristic of the disease.

During a preliminary period of not less than 4 weeks all the sprue patients tested were given a diet which contained almost no fat and limited carbohydrates, but which was rich in its content of

proteins and fresh fruit, a diet widely accepted in the treatment of sprue. During this control period the intake of fat was made constant before the test was made. In no instance were the patients symptom-free on this régime, although all were considerably better than was the case when a general diet containing lipid was taken.

The amounts of lipid in the blood of all 5 cases of sprue showed practically no increase following the fat meal (Figs. 3, 4). This fact, coupled with the well known observation that a large amount of fat is present in the intestinal contents, seems to be adequate evidence that the absorption of fat is interfered with in the active phases of the disease even though anemia and stomatitis are not present.

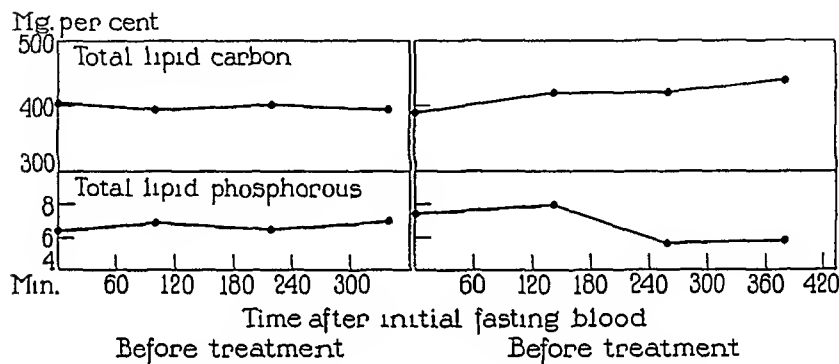


FIG. 4.—Blood-lipid curves of 2 sprue patients following fat meal before liver-extract treatment.

The 3 cases which were tested again after treatment with liver extract injected intramuscularly showed wholly different amounts of lipid in the blood. All clinical symptoms were then quiescent. In Case 2 one injection of liver extract (10 cc. Lilly N.N.R., derived from 50 gm. of liver) was sufficient, whereas in the other cases several injections repeated daily were required. In all 3 cases a pronounced rise in the level of the total lipid carbon resulted, and the resultant curve approached normal in both duration and height, presenting a striking contrast to the practically flat curves obtained before treatment.

Discussion. From the results which have been presented it seems to be clear that normal individuals react to a meal containing 2 gm. of fat per kilo of body weight by a pronounced and well sustained increase of the amounts of lipid in the blood. Patients with sprue, on the other hand, still manifesting symptoms after treatment with diets low in the content of fat, exhibit no such increase under similar experimental conditions. If treatment with liver extract, parenterally administered, is instituted, however, amelioration of symptoms results and a normal increase in the levels of lipids in the blood fol-

lows the taking of the same amount of fat, which was ingested previously.

The passage of bulky loose stools follows the taking of a test meal of fat before treatment with liver extract, but this does not occur during the 6-hour period of the test, but only from 12 to 48 hours after the experiment has been terminated. This time relationship of diarrhea to the withdrawal of blood samples for analysis suggests that the lack of increase of the content of the blood lipid cannot be ascribed to loss of fat from the intestinal canal, but to an actual failure of absorption by the intestinal mucosa. It is to be inferred from this observation that malabsorption results in diarrhea rather than that diarrhea is the cause of malabsorption. This conclusion is substantiated by the fact that diarrhea ceases on the parenteral administration of liver extract and is associated with normal amounts of lipid in the blood after the taking of a meal of fat. This observation suggests not only that remissions in sprue are associated with return of normal absorption of fat, but also that liver extract exerts some specific effect in converting malabsorbing intestines to normal function. It might be supposed that improvement was due to some alteration in bile salts, were it not for the observation of Thaysen⁸ that the bile salt content of the duodenal contents is perfectly normal in patients with sprue.

Thaysen has administered bile salts furthermore to such patients without affecting the excretion of fat, while Starr and Gardner⁷ found no decrease of the fat excretion of patients with sprue during the oral administration of bile. Although the effect of liver extract in promoting absorption from the intestinal tract in patients with sprue requires further investigation, it seems probable that the effect is a direct one upon the intestinal wall. This assumption is strengthened by the report of Fairley that the absorption of sugar from the intestinal tract is subnormal in such cases during relapse but improves after treatment. Unfortunately, his cases are not strictly comparable to ours for they were treated by a combination of restricted diet and liver extract orally administered, so that the effect due to either diet or liver extract alone cannot be estimated. Our cases were followed on the usual régime of restricted fat and carbohydrate intake sufficiently long to establish the facts that the absorption of fat was below normal on such régimes and that it was improved by the injection of liver extract.

Conclusions. 1. The levels of fat in the blood after the ingestion of a meal rich in fat have been determined for normal subjects by the method of Kirk, Page and Van Slyke.

2. Five cases of sprue studied during the presence of intestinal symptoms showed an absence of the normal increase in the levels of fat in the blood after a fat meal.

3. Three of the 5 cases were tested after the parenteral adminis-

tration of liver extract and showed postabsorptive levels of fat in the blood which approached the normal.

4. The experimental results suggest that in sprue, liver extract exerts some specific effect upon the absorptive power of the intestinal tract.

REFERENCES.

- (1.) Castle, W. B., Rhoads, C. P., Lawson, H. Q., and Payne, G. C.: *Arch. Int. Med.*, 56, 627, 1935. (2.) Fairley, N. H.: *Trans. Roy. Soc. Trop. Med. and Hyg.*, 30, 9, 1936. (3.) Kirk, E. F., Page, I. H., and Van Slyke, D. D.: *J. Biol. Chem.*, 106, 203, 1934. (4.) Mackie, T. T., Miller, D. K., and Rhoads, C. P.: *Am. J. Trop. Med.*, 15, 571, 1935. (5.) Man, E. B., and Gildea, E. F.: *J. Biol. Chem.*, 99, 61, 1932. (6.) Miller, D. K., and Rhoads, C. P.: *Am. J. Med. Sci.*, 191, 453, 1936. (7.) Starr, P., and Gardner, L.: *Am. J. Trop. Med.*, 10, 283, 1930. (8.) Thaysen, T. E. H.: *Non-tropical Sprue*, Copenhagen, Levin and Munksgaard, 1932.

PROTAMINE INSULINATE IN THE TREATMENT OF DIABETES IN PSYCHOTIC PATIENTS.

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THE treatment of diabetes in psychotic patients offers many problems that are not found in the usual diabetic clinics of the general hospital.

These patients are frequently uncoöperative and almost without exception are prone to pilfer food. Many times they strenuously object to being given their injections so that the excitement aroused by this procedure three times a day serves to elevate their blood sugar levels still further. For these reasons the charts of the diabetic patients show great fluctuations in blood sugar levels and urinary sugar excretion. When the laboratory reports a very high blood sugar level, the insulin may be increased in an effort to reduce it, and subsequently a dangerously low level may result. Any method which can reduce the number of injections required and afford a continuous supply of insulin throughout the day would be particularly beneficial in the treatment of these patients. This seems to have been accomplished by the use of protamine compounds of insulin by Hagedorn and his co-workers.^{3a}

The new compound and its zinc modification have been studied by various investigators (Hagedorn,^{3b} Joslin,⁴ Joslin, *et al.*,⁵ Rabinowitch, *et al.*,^{6,7} Root, *et al.*,¹⁰ Sprague, *et al.*,¹¹ Campbell, *et al.*,² Richardson and Bowie⁹). The beneficial effects and the decrease in both number of injections and total amount of insulin needed seem

to be firmly established by their work. Certain precautions against overdosage and the insidiousness of hypoglycemic symptoms have been emphasized by Allen.¹ Richardson² has described the advantages of protamine zinc insulin and given detailed directions for its use.

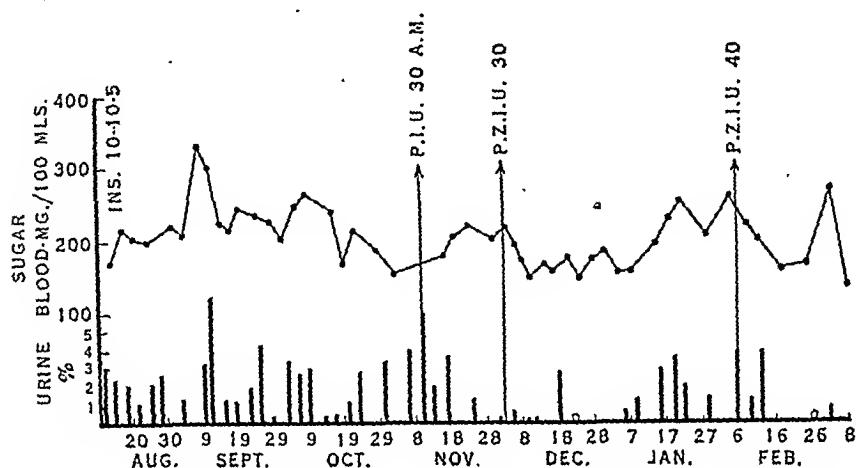


CHART I.—J. P., age, 58; weight, 185; duration, 8 years; diet, C. 200; P., 180; F., 100; D. P., hebephrenic.

Since August, 1936, we have been utilizing various preparations of Protamine Insulinate and Protamine Zinc Insulinate* in the treatment of 4 diabetic male patients. A single injection was given before breakfast and the diet was evenly distributed through the three meals. A brief clinical account of each patient follows:

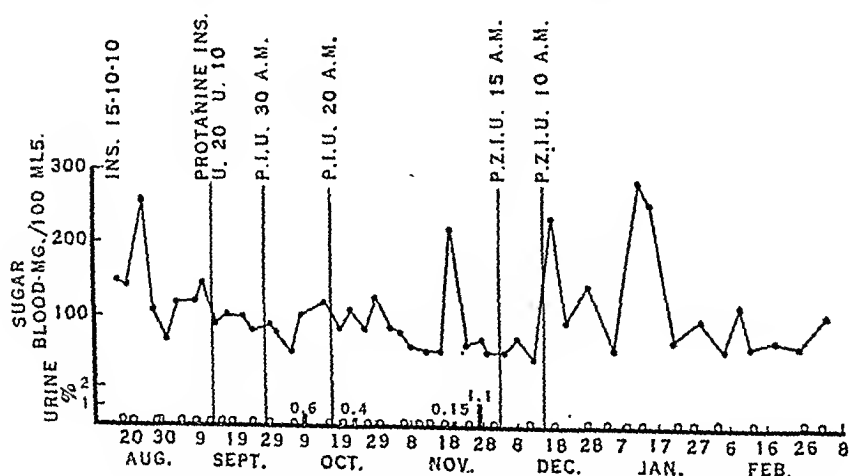


CHART II.—O. C., age, 66; weight, 112; duration, 9 years; diet, C. 138; P., 78; F., 138; PSY., with psychopathic personality.

Case Abstracts. CASE 1.—O. C., male, white, aged 66, was admitted to this hospital March, 1915. Diagnosis: psychosis with psychopathic personality. He also had syphilis and was given antiluetic treatment. He was first noticed to have diabetes and moderately advanced pulmonary tuberculosis in 1932. Physical examination revealed moderate peripheral

* This material was supplied through the courtesy of Eli Lilly & Co.

arteriosclerosis with blood pressure of 128/92. The urine contained sugar and the blood sugar was elevated. He was put on a diabetic diet of carbohydrates 138, protein 78, fat 138, and insulin 15-10-10 units. Considerable difficulty was experienced in controlling the diabetes because of the patient's

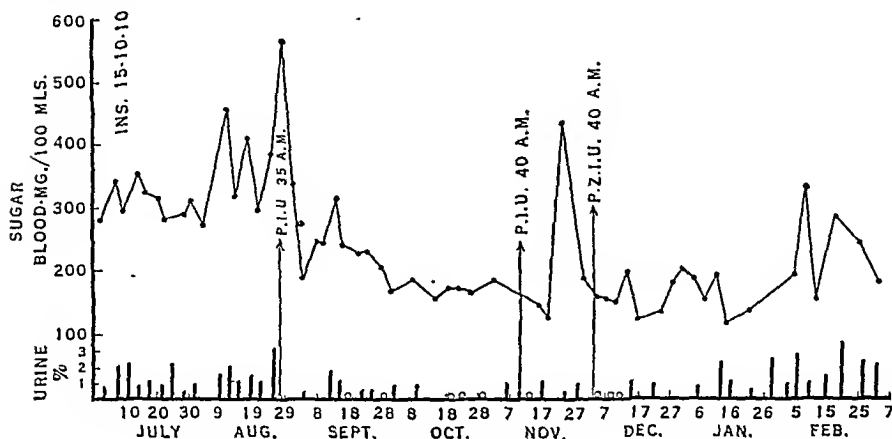


CHART III.—R. K., age, 58; weight, 160; duration, 6 years +; diet, C. 200; P. 60; F. 100; general paresis.

uncoöperativeness in taking food from other patients' trays. His blood sugar varied from 80 to 250. The urinary sugar varied from zero to 0.6%. September 15, 1936, he was started on protamine insulinate, 30 units daily. The blood sugar gradually became lower and showed much less fluctuation. On November 25 insulin was cut to 15 units and on December 15, 1936, to 10 units daily. Except for an occasional fluctuation the blood sugar is now between 70 and 100 and urine is sugar-free.

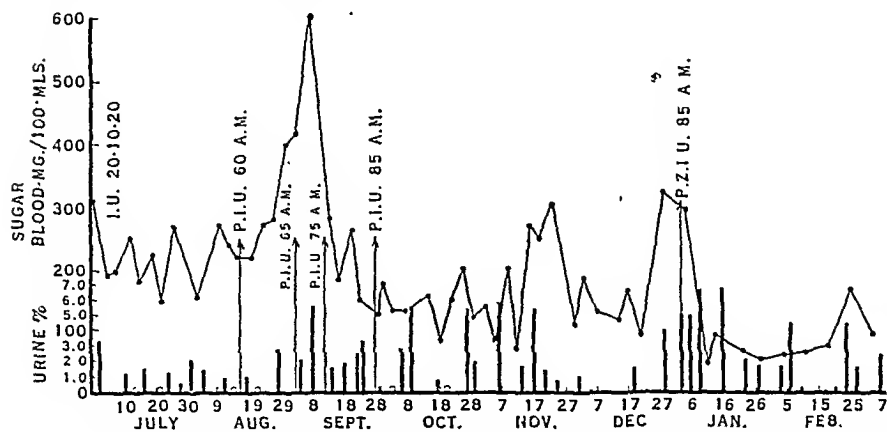


CHART IV.—J. S., age, 50; weight, 133; duration, 9 years; diet, C. 150; P. 70; F. 100; D. P., paranoid.

CASE '2.—J. P., male, aged 58, admitted to this hospital July, 1921, was diagnosed as a case of dementia præcox, hebephrenic type. He was first noticed to have diabetes in 1929, with sugar in his urine and blood sugar elevated. Physical examination showed heart and lungs to be normal and

blood pressure 150/90. On a diet of carbohydrates 200, protein 80, fat 100 and insulin 10-10-5 units, the blood sugar fluctuated from 150 to 325 and the urine contained from 1% to 10% sugar. The patient was uncoöperative, stealing food from other patients. On November 10, 1936, he was placed on protamine insulin, 30 units, and the same diet followed. The blood sugar showed less fluctuation, varying from 150 to 210. On December 1, 1936, protamine zinc insulin was started and for 1 month the blood sugar remained between 150 to 160, then the sugar began to rise to 250. Protamine zinc insulin increased to 40 units February 6, 1937. The blood sugar is still fluctuating, but is tending to return to a normal level.

CASE 3.—R. K., male, white, aged 50, was admitted to this hospital October, 1931, because of dementia paralytica and diabetes mellitus. Physical examination showed moderate peripheral sclerosis, blood pressure 150/90, heart and lungs normal, pupils not reactive to light. The blood and spinal fluid gave positive Wassermann reactions for which he received anti-luetic treatment. On a diet of carbohydrates 200, protein 60, fat 100, with insulin 15-10-10 units, the diabetes was very difficult to control. Blood sugar varied from 260 to 564 and urine at times contained as much as 3% sugar. In August, 1936, the patient developed a cellulitis of the left leg and a beginning gangrene of the left heel. He was placed on protamine insulinate, 35 units in A.M., on August 27, 1936. The blood sugar went steadily to 160 and the condition of the leg improved. On November 10, 1936, protamine insulinate was increased to 40 units. Protamine zinc insulin was started on December 3, 1936. Blood sugar after this was consistently below 200 until February, 1937, when the patient was allowed off Medical Service. Since then the blood sugar has again become irregular, varying from 150 to 320 and the urine contains from 1 to 3% sugar. This variation is due undoubtedly to the patient's taking food from other trays.

CASE 4.—J. S., male, white, aged 50, was admitted to this hospital March, 1919. Diagnosis: dementia præcox, paranoid type. He was first discovered to be a diabetic in 1929. Physical examination showed that the heart and lungs were normal and blood pressure 136/88. He was placed on a diet of carbohydrates 150, protein 70, fat 100, with insulin 20-15-20 units. The blood sugar varied from 310 to 250 and urine sugar from zero to 3.5%. Protamine insulinate was started August 16, 1936, 60 units in A.M. The blood sugar showed a steady climb, reaching a height of 600. The insulin was increased up to 75 units, when blood sugar began to come down, and on September 28, 1936, 85 units were given daily. Blood sugar on this dosage became fairly stable around 150, but urine still contained from 3% to 6% sugar. On January 3, 1937, protamine zinc insulin was started, 85 units in A.M., and the blood sugar became much lower, all figures being below 100. In spite of this low blood sugar, the urine still contained from 2% to 4% sugar.

Discussion. In one case a smaller dosage of insulin was accompanied by a lower blood sugar level; in the other 3 the dosage of protamine insulinate was increased above that of unmodified insulin, but the fluctuations in blood sugar were markedly diminished. In one patient, J. S., in whom the excretion of sugar continued even though the blood sugar level fell well below the normal value of 100 mg. %, an abnormally low sugar threshold appeared to be responsible. In his case the change to protamine zinc insulinate was definitely of value, as for the first time consistently low values were obtained for his blood sugar.

The use of protamine zinc insulinate was admittedly subjected

to a very severe test in these 4 cases. In 2, the diabetes was associated with lues; one also with tuberculosis. In all cases a definite improvement in the physical condition of the patients was seen, and a decrease in the marked fluctuations in the blood sugar levels.

On the basis of these experiments it has been decided to extend the use of the protamine zinc insulin to all diabetics requiring more than a single injection of unmodified insulin to control their blood sugar level, as the slow release of insulin is able to compensate for the uncoöperativeness of the patients with respect to diet.

Summary.—Four diabetic psychotic male patients were treated with protamine insulinate and protamine zinc insulinate. It was found that this treatment was more satisfactory than the use of regular unmodified insulin, resulting in a decrease in the fluctuations in blood sugar levels and in one case in a reduction of insulin requirements from 35 to 10 units daily.

REFERENCES.

- (1.) Allen, F. M.: *J. Am. Med. Assn.*, **107**, 430, 1936. (2.) Campbell, W. R., Fletcher, A. A., and Kerr, R. B.: *AM. J. MED. SCI.*, **192**, 589, 1936. (3.) Hagedorn, H. C., Jensen, B. N., Krarup, N. B., and Wodstrup, I.: (a) Protamine Insulinate. Seventeenth Med. Cong. North Countries, Copenhagen, June 27, 1935; (b) *J. Am. Med. Assn.*, **106**, 177, 1936. (4.) Joslin, E. P.; *Ann. Int. Med.*, **10**, 179, 1936. (5.) Joslin, E. P., Root, H. F., et al.: *New England J. Med.*, **214**, 1079, 1936. (6.) Rabinowitch, I. M., Foster, J. S., et al.: *Canad. Med. Assn. J.*, **35**, 239, 1936. (7.) Rabinowitch, I. M., Fowler, A. F., and Corcoran, A. C.: *Ibid.*, p. 124. (8.) Richardson, R.: *AM. J. MED. SCI.*, **193**, 606, 1937. (9.) Richardson, R., and Bowie, M. A.: *Ibid.*, **192**, 764, 1936. (10.) Root, H. F., White P., et al.: *J. Am. Med. Assn.*, **106**, 180, 1936. (11.) Sprague, R. G., Blum, B. B., et al.: *Ibid.*, p. 1701.

CORONARY THROMBOSIS WITHOUT PAIN.

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PRACTICALLY all discussions of the clinical features of coronary artery disease have cardiac pain as their central theme. This emphasis, entirely justified, has created coronary artery-consciousness so that occlusion of these vessels, formerly often overlooked because of atypical pain, at present may be diagnosed when other painful syndromes are actually present. But in both situations it is pain which plays the leading rôle.

Evidence is rapidly accumulating to show that coronary thrombosis may occur without pain; in fact, qualified observers have suggested that painless coronary episodes are about as frequent as the

dramatic painful accidents. These estimates, based upon post-mortem material, contain an obvious source of error, namely many patients are too ill to permit detailed inquiry and the record may be inadequate on the subject of pain. Nevertheless painless coronary thrombosis must be fairly common, since one-third of our patients with proven coronary thrombosis manifested no pain, although this point was the subject of particular interrogation in the last 127 cases coming under our observation. This percentage excludes patients whose condition did not permit a detailed history to be taken. In view of the frequency of coronary thrombosis, this aspect of the subject would seem to have been neglected if brevity of discussion in monographs and paucity of the reported instances in medical literature may be employed as criteria.

The purpose of this paper is not to report hitherto unknown facts but to direct attention to an apparently common but seemingly neglected aspect of an important problem. Seven cases of this nature, reported as briefly as possible, have been selected to illustrate some of the clinical pictures encountered.

Clinical Abstract. CASE 1.—A. W., a 61-year-old Jewish male salesman was admitted for convalescent care on February 5, 1937. On August 6, 1936, he was seen at an allied hospital because of an attack of "asthma" of a few hours' duration. For a few weeks prior to the attack there had been exertion dyspnea, occasional nocturnal dyspnea and slight ankle edema; otherwise he had been well. A diagnosis of coronary thrombosis was made upon electrocardiographic evidence and he remained in the hospital for 6 weeks because of dyspnea, orthopnea and malleolar edema. Gradual improvement occurred and he was discharged to a convalescent home. After some time the symptoms reappeared, requiring re-hospitalization; upon improvement he was transferred to Metropolitan Hospital. He stated that he had never experienced any precordial, abdominal, neck or arm pain and that he had not had any gastro-intestinal disturbances. At this time he was free from dyspnea although some nocturnal distress had been present for 3 nights prior to admission.

Examination revealed a fairly well-developed and well-nourished male lying flat in bed. There was no dyspnea, cyanosis or edema. The neck veins were not distended. The left border of the heart was 2 cm. beyond the nipple line and the cardiac sounds were distant. A soft systolic murmur was heard at the apex and transmission to the axilla noted; a few premature contractions were observed. The lungs and abdomen were negative, the extremities free from edema; the brachial vessels were thickened. Blood pressure, 100/56; temperature, 98.6° F.; pulse, 80. The blood Wassermann reaction was negative and the blood chemistry normal. The urine contained a trace of albumin and a few hyaline casts; the specific gravity was 1.018. Sedimentation of the red blood cells 1 mm./hr.; leukocytes numbered 6900. The electrocardiogram on admission is reproduced in Figure 1.

On January 23 at 8 P.M. he suddenly became very dyspneic and weak following an attempt to defecate. His face was pale, the expression apprehensive, the lips cyanotic and there was marked orthopnea. The neck veins were distended. No pain experienced. Blood pressure, 60/30 (?), rate rapid but regular; heart sounds of poor quality, very distant and a suggestion of gallop rhythm. Râles were noted at the bases of the lungs.

On the next day the liver was palpable 3 fingers below the costal margin and edema of the legs had appeared. Blood pressure, 60/?. The tem-

perature was 102° F.; leukocytes numbered 16,800 with 82% neutrophils; sedimentation time, 64 mm./hr. The electrocardiogram now showed a radical change. The presence of a Q wave in L_1 and small upward deflection, prominent S wave in L_2 and deep S wave in L_3 and the absence of definite bundle-branch block (QRS interval, 0.10) suggest myocardial infarction in the territory of the anterior coronary artery (Fig. 2). The patient went steadily downhill and died, January 25, 1937.

Autopsy Extract. "The heart and aorta weighed 1050 gm. The epicardium was markedly infiltrated with fat, the coronary vessels somewhat tortuous. On the posterior aspect of the left ventricle there is a slight deposit of fibrin. An area of softening, about the size of a dime is seen midway between the base and apex, about 1 cm. from the interventricular groove. The myocardium of the right ventricle is 5 mm. in thickness, the pulmonary valve normal. The intima of the pulmonary artery is normal except for patches showing hemolysis. The myocardium of the left ventricle is 1.5 cm. in thickness. There is slight hardening of the base of the aortic ring. The coronary orifices were normal. The thoracic aorta revealed some lipoidal infiltration and scattered atheromatous plaques. Among the trabecula of the left ventricle there are some adherent thrombi. The mitral valve is normal. The right auricular appendage is empty.

"On section the myocardium has a decidedly pale, parboiled appearance. An area of softening corresponding to the area mentioned on the posterior aspect of the left ventricle extends into the myocardium. The coronary arteries are sclerotic, but an actual thrombus was not observed. The anatomical diagnosis was coronary thrombosis, myocardial infarction, thromboendocarditis, aortic and renal arteriosclerosis."

Comment. An elderly male was observed during two episodes of myocardial infarction. A completely negative past history suggests that he belonged to the group of so-called "latent coronary artery disease." His first major coronary accident was not associated with pain but with an equivalent in the form of "asthma" superimposed upon mild cardiac failure. The second episode followed slight exertion and was likewise free from pain; otherwise the symptomatology was not unusual.

CASE 2.—P. E. (No. 437), a 77-year-old white female, entered the hospital, March 16, 1936. For the past 3 years she had experienced dyspnea on exertion and occasionally at rest; transient edema of the ankles and rare attacks of nocturnal orthopnea developed at the same time. She emphasized that these attacks were always painless, occurred after exertion and consisted of "gasping for air and much sweating." She also had noted attacks of vertigo and black spots before the eyes. In 1934, she was hospitalized for dyspnea and discharged improved; at that time she was informed of the existence of hypertension. More recently there has been nocturia and increased urinary frequency during the day. Very recently her vision has been failing. Throughout the past year she has attended cardiac clinic. The night before admission she suddenly became dyspneic and was compelled to gasp for air. The difficulty persisted and she called an ambulance the following morning.

Examination revealed an elderly white female, markedly dyspneic and orthopneic. The fundi showed tortuous and narrowed arteries. The neck veins were distended. Moist râles were heard over both bases. The blood pressure was 190/110. The heart was enlarged to the left and a rough systolic murmur was audible over the entire precordium, loudest at the apex. The pulmonic second sound was accentuated; heart sounds of fair

quality, rate 108. The peripheral vessels were sclerotic. The liver edge was felt 2 fingers below the costal margin. The extremities showed a few varicosities and no edema. She was regarded provisionally as an instance of "arteriosclerotic heart disease with marked left- and mild right-sided failure with passive congestion" and treated accordingly.

On the day after admission the temperature rose to 101° F. and remained somewhat elevated for the next 10 days; dyspnea and orthopnea gradually increased, more râles were noted in both lung fields, peripheral edema increased. On March 28 she became mentally confused and remained so until death, on April 16. The blood pressure was variable, usually somewhat lower than on admission, once rising to 200/135 and near the end approximating 155/90. The blood Wassermann reaction was 1+, the blood chemistry normal; the urine revealed a trace of albumin and a few granular casts. Concentration tests showed a fixation of specific gravity between 1.016 and 1.018. The white blood cell counts averaged 14,000, with 84% neutrophils. The sedimentation times were 40 mm./hr. (March 17) and 90 mm./hr. (April 9).

On March 16 the electrocardiogram was as follows: rate 104, L.A.D. T_1 diphasic. $P-R$ interval 0.20; March 20, the rate 78, L.A.D., $P-R$ interval 0.24. L_1 and L_2 $S-T$ depressed. P waves very small in L_1 , L_2 , L_3 . The change was regarded as due to digitalis.

At autopsy the heart and aorta weighed 620 gm. The aortic ring revealed marked hardening and the aorta showed many atheromatous patches. The coronary vessels were decidedly sclerotic, tortuous, but patent except the left descending branch which was obliterated. On section, the myocardium, in the area supplied by the left descending branch, shows an extensive whitish patch with transverse striations. Microscopic examination revealed a healing infarct of the myocardium.

Comment. An elderly female with known hypertension, arteriosclerotic heart disease, mild congestive and left ventricular failure entered the hospital for relief of dyspnea. Similar episodes had occurred before, but this time the attack persisted. There was no pain, the blood pressure did not fall, but the sedimentation velocity had increased. The electrocardiogram presented changes compatible with known prolonged administration of digitalis. During her brief hospitalization the passive congestion increased and the picture suggested a terminal bronchopneumonia superimposed upon hypostasis. Postmortem examination revealed coronary thrombosis, myocardial infarction (healing stage), and passive congestion of the lungs.

In retrospect it has seemed to the writers that coronary infarction occurring in the course of congestive failure is often not associated with pain. It is generally known that the pain of "angina pectoris" tends to disappear when congestive failure occurs, but it does not seem equally widely appreciated that pain may not be present even when major coronary artery accidents occur during congestive failure.

CASE 3.—A. M. (No. 984), a white Italian female of 70, entered the hospital, November 19, 1936. For the last 7 years she has had exertion dyspnea but no symptoms when at rest. Intermittent edema of the ankles has been present during the same period. No precordial pain has ever been present; hypertension has existed for several years. About 2 weeks

before admission the dyspnea became decidedly worse, marked orthopnea developed and ankle edema increased.

The patient was an elderly white, markedly dyspneic and orthopneic female. Cyanosis of the lips and nose noted. Bilateral cataracts exist. There was decided fullness of the neck veins. Impaired resonance over both lung bases and moist râles in the same areas. Blood pressure 138/78, rate rapid. The heart sounds are hardly audible owing to the chest noises. The pulse was weak in quality and irregular in rhythm. The peripheral vessels were sclerotic. The liver edge was palpable 2 fingers below the costal margin and tender. Marked pitting edema of the lower extremities up to the knees.

The temperature was normal on admission but it rose to 100° F. later in the day, to 101° F. on the following day and 100° F. on the third, the day of her death. The pulse ranged between 100 and 120. Sedimentation 90 mm./hr. On the second day the blood pressure fell to 88/46 and she lapsed into coma from which she did not recover. The electrocardiogram briefly was as follows: normal sinus rhythm, rate 108. *P-R* interval 0.20. No axis deviation. *QRS* complexes very small in all leads. *P* and *T* waves also very small in all leads.

Autopsy. The heart weighed 450 gm. "Within the left ventricle at the apex there is a very soft thrombus adherent to the wall. When the thrombus was removed, the myocardium appeared to bulge, not unlike a cardiac aneurysm. At the center of the bulging area, the myocardium is about 1 mm. thick. The myocardial softening extends a short distance beyond the area occupied by the thrombus. The mouths of the coronary vessels are narrowed and the vessels are sclerotic. At 2 cm. from the origin of the left descending coronary artery the lumen is obstructed by a recently formed thrombus. The aorta shows many calcified plaques." (For microscopic report see later.)

Comment. As in the preceding case the correct antemortem diagnosis was not established. In retrospect coronary thrombosis ought to have been considered in view of our inability to explain satisfactorily the sudden aggravation of her symptoms. It is also of interest to note that 3 of the cases reported here are elderly hypertensive females. In our experience, Cases 2 and 3 represent the most common syndrome of "painless" coronary thrombosis, namely, unexplained aggravation of dyspnea occurring during the course of congestive heart failure.

CASE 4.—M. R. (No. 987), a white female dressmaker, aged 55, was admitted to the hospital, November 15, 1935, at 1 p.m. As she was in coma no history could be obtained. The landlady who accompanied her stated that the patient had been found lying unconscious on the floor of her room. A few hours earlier the patient had seemed to be entirely well and no outcry had been heard in the adjoining room.

The patient was an emaciated comatose white female. The cheeks were ashen, the lips and fingers cyanotic, the extremities cold and covered with clammy perspiration. Temperature normal; pulse, 110; respirations, 24; blood pressure, 110/70. No marks of violence on the body and no evidence of skull injury. The pupils were slightly contracted and reacted poorly to light and accommodation. No odor to the breath. The neck veins were distended. Auscultation of the lungs revealed numerous fine moist râles throughout the lower two-thirds of both lungs. The left border of the heart was 3 cm. beyond the nipple line; the heart sounds were poor in quality and the first sound roughened at the apex; occasional premature con-

tractions. Moderate sclerosis of the brachial vessels and a few varicosities of the lower extremities were recorded. The abdomen was negative. Since she was found in collapse without a history of previous illness, her appearance, rapid pulse, weak heart sounds, a diagnosis of coronary thrombosis was suggested and corresponding therapy initiated. Later in the day she improved considerably. She stated that she had been feeling perfectly well, had suddenly become dizzy, and "must have lost consciousness." Several years ago she had been informed of the existence of hypertension and during the last 2 years had experienced several attacks of precordial pain. For the last year she had suffered from numerous headaches, occasional attacks of vertigo, exertion dyspnea and insomnia. That night the cyanosis diminished and her color improved. The blood pressure remained unchanged. The white blood cell count was 10,500 with 77% neutrophils; the red blood cells numbered 4,440,000; sedimentation time 1 mm./15 min. A friction rub was now audible in the third left interspace over the precordium. As the electrocardiograph was out of order, no tracing was secured. The next morning her condition became poor. The pulse was rapid and weak and she died at 8 A.M., about 30 hours after admission.

Autopsy. The epicardium showed abundant fat. The mitral, pulmonary and tricuspid valves were normal; some sclerosis at the base of the aortic valve. The left ventricle measured less than 1 cm. in thickness. At the apex it was somewhat thinner, very flabby, and covered by a thick layer of fat. On section, the myocardium showed a large patch with whitish striations, this patch being paler and softer in consistency than the remainder of the myocardium; the corresponding layer of endocardium had lost its luster. The coronary arteries were markedly sclerotic; the anterior branch of the left descending artery was occluded by a thrombus; the smaller branches were sclerotic and obliterated.

Comment. Several cases of this type could have been included. In some there is sudden marked vertigo followed by extreme weakness. As in the other cases no history of pain could be obtained at the time of the illness.

CASE 5.—P. F. (No. 1030), a 53-year-old white laborer, entered the hospital, October 28, 1936. Two hours before admission while sitting in his room he suddenly experienced marked breathlessness, weakness and then fainted. He recovered consciousness in a few minutes and noticed, in addition to breathlessness, that he was bathed in cold perspiration. He felt very apprehensive and weak. There was no pain but decided palpitation: "the heart was fluttering." Slight nausea followed. He informed the ambulance physician that the fluttering had diminished but the weakness and breathlessness persisted: "I feel as if I were suffocating." Two years before admission he had been informed of the existence of hypertension and had sought medical aid for "attacks of fluttering in the heart" which appeared on exertion. There had never been any edema, nocturnal dyspnea nor gastro-intestinal complaints. No further history was attempted because of his poor condition but detailed inquiry on the subject of pain failed to elicit any presence of this symptom.

Examination revealed an obese white male with marked respiratory distress and orthopnea. The face was ashen, lips and extremities cyanotic. He appeared apprehensive and answered questions in a weak, husky voice. The neck veins were distended. The lower two-thirds of both lungs were filled with moist râles. The heart was enlarged to the left and the sounds of poor quality, "tick-tock rhythm." The rate was rapid and the heart irregular. No murmurs were detected. The abdomen was soft and the liver just palpable. No clubbing or edema of the extremities but defi-

nite coldness and cyanosis. Temperature, 97° F.; pulse, about 160; respiration, 38; blood pressure, 125/100. The probable diagnosis seemed coronary thrombosis; an immediate electrocardiogram revealed auricular fibrillation; ventricular rate, 150. *QRS* of marked amplitude in *L*₂ and *L*₃. Ventricular premature contractions. Slight depression of *S-T* segment in *L*₁, high take-off of *S-T* segment in *L*₂ and *L*₃. One hour after admission the blood pressure was 70/? and 30 minutes later the patient was dead.

Owing to the fact that the patient had recently participated in a fight, the body was sent to the Medical Examiner. A telephonic report informed us that a fresh thrombosis was found in the posterior descending artery.

Comment. This patient, like the preceding, gave a history of hypertension and he had been cardiac conscious for 2 years. Exclusive of the absence of pain, he presented the usual features of coronary thrombosis.

CASE 6.—B. J. (No. 208), a 62-year-old colored laborer, entered the hospital, February 5, 1937. In 1929, he noted dyspnea on exertion and shortly afterwards orthopnea, nocturnal dyspnea, and slight edema of the extremities. These symptoms appeared intermittently and improvement coincided with visits to a dispensary. Several years ago as well as 2 months before hospitalization he was informed of the existence of hypertension. In 1935, he was hospitalized for decompensation and about that time he complained of slight precordial pain, radiating to the left shoulder which lasted for a few minutes. It was not severe and never recurred. Three weeks ago he had a slight "cold." Otherwise the history is negative, in fact, it was singularly free from previous illnesses, although hemorrhoids were present for a short time several years ago. He is the son of a white father and a half-white mother. The night before hospitalization, just before retiring, he experienced a sudden severe choking sensation in the throat together with marked weakness, faintness and dyspnea. This persisted through most of the night, gradually diminishing in severity. There was no associated pain.

The examination revealed a well-developed, somewhat undernourished, elderly, light colored negro who was markedly dyspneic and orthopneic. The neck veins were distended and the chest emphysematous. Moist râles were heard throughout both lung bases. Blood pressure, 130/90. The left border of the heart was in the anterior axillary line, sounds distant. There was normal sinus rhythm and a short harsh systolic murmur was heard at the apex. The brachial vessels were sclerotic. The liver edge was palpable 3 fingers below the costal margin. No edema or clubbing of the extremities. A few external hemorrhoids were noted.

The electrocardiogram on admission is shown in Figure 3, and 3 days later (February 8) in Figure 4. On February 15: *P-R* interval, 0.22. Deep *Q* wave in *L*₂; definite *W*-shape of *QRS* in *L*₃; *S-T* rounded and high take-off in *L*₂, *L*₃. *L*₅, absence of initial downward deflection.

The diagnosis of acute coronary occlusion was made on the basis of acute onset, relatively low blood pressure and the electrocardiographic findings. He improved somewhat during the first few days, but then dyspnea and orthopnea increased, edema of the extremities developed, additional râles in the lungs were evident. He went steadily downhill and died 19 days after admission. No autopsy was permitted.

Extracts from the laboratory and other reports follow: On admission: temperature, 97° F.; pulse, 100; respiration, 30. On the following day the temperature rose to 101° F., then down to 100° F. for 1 week and then normal. The pulse was constantly about 100. The initial blood pressure

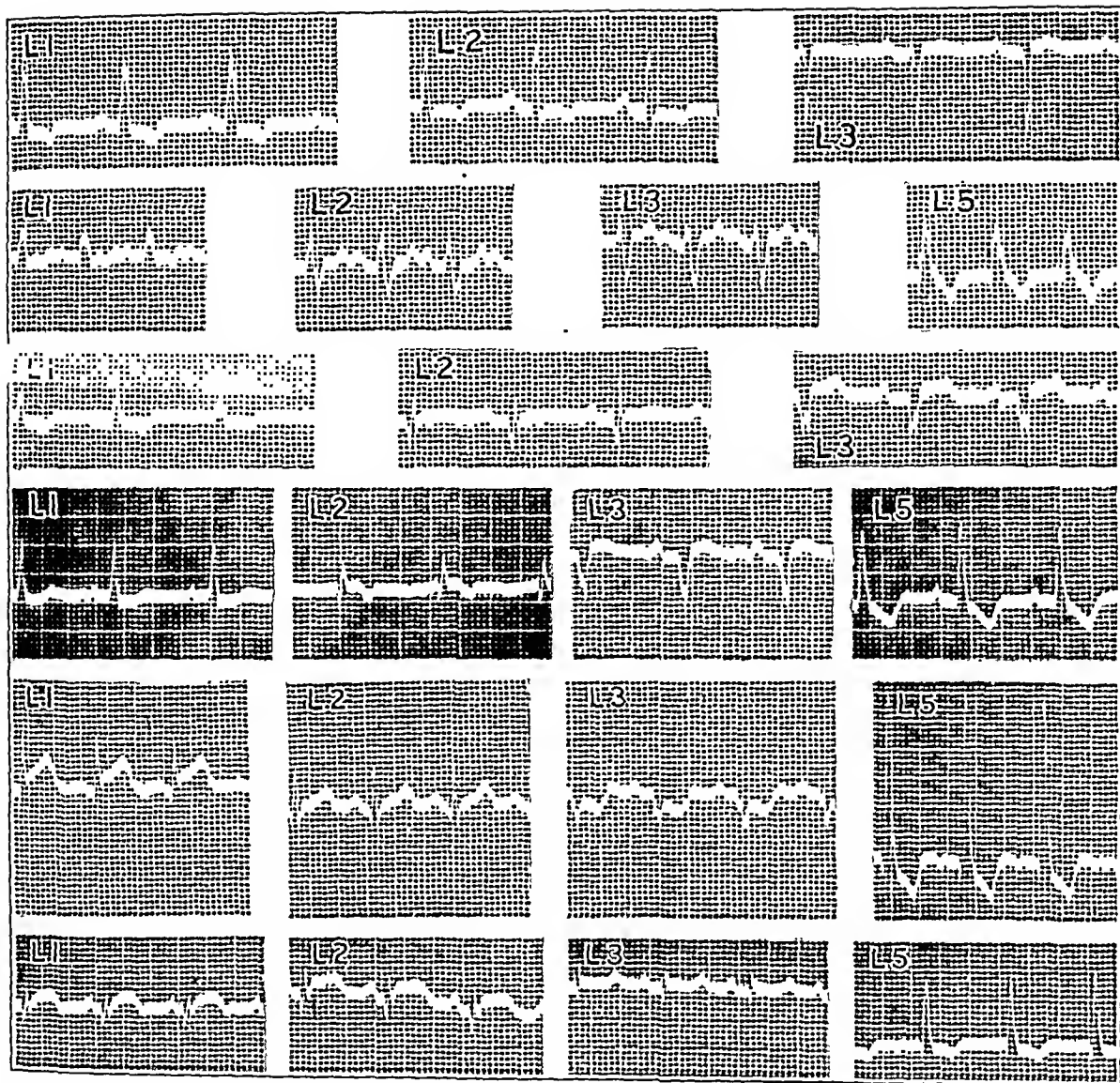


FIG. 1.—Case A. W. (December 20, 1936.) Electrocardiogram shows regular sinus rhythm 80/min. $S-T_1$ and $S-T_2$ segments slightly depressed, $S-T_3$ rounded. T_1 inverted and T_2 coved.

FIG. 2.—Case A. W. (January 23, 1937.) Electrocardiogram shows sinus tachycardia rate 130/min. QRS complexes small; $P-R$ interval 0.20 Q_1 present; S_2 and S_3 prominent; T_1 diphasic. In L_5 initial downward deflection very small.

FIG. 3.—Case B. J. (February 5, 1937.) The electrocardiogram shows normal sinus rhythm, rate 88/min. $P-R$ interval 0.20; QRS small; tendency to "W" shaped Q in L_3 . $S-T_1$ depressed and slightly elevated take-off of $S-T_3$. T_1 diphasic and T_2 almost isoelectric.

FIG. 4.—Case B. J. (February 8, 1937.) Electrocardiogram shows definite Q_2 . $S-T_3$ segment rounded. In L_5 initial downward deflection absent.

FIG. 5.—Case H. P. (October 28, 1936.) Electrocardiogram shows normal sinus rhythm, rate 109/min. High take-off of $S-T_1$, with large T wave. $S-T_2$ slightly elevated. Markedly depression of $S-T_3$. In L_5 the initial downward deflection is very small.

FIG. 6.—Case H. P. (November 4, 1936.) Electrocardiogram shows QRS complexes small in all leads. In L_1 and L_2 $S-T$ segment rounded with a high take-off and $S-T_3$ almost isoelectric. T_3 small and upright. In L_5 initial downward deflection is very small and upward deflection is smaller than previous E.C.G. (Fig. 5) and T wave is isoelectric.

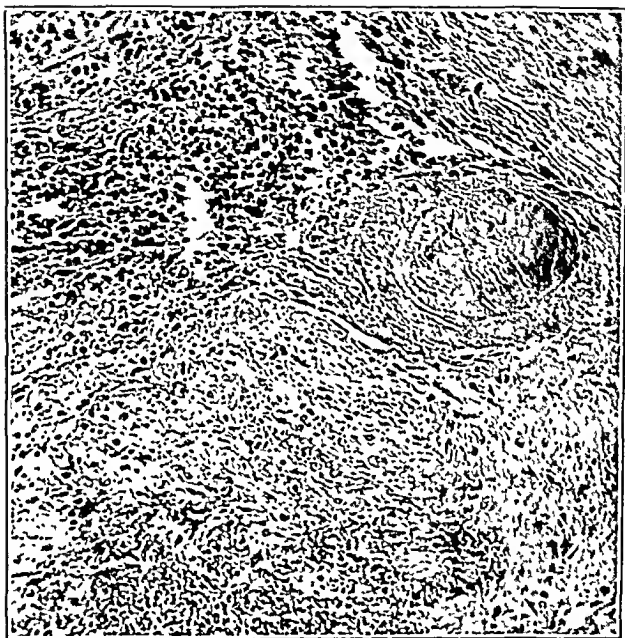


FIG. 7.—Myocardial infarction. Case 3. Vascular thrombosis, proliferating fibrous tissue, focal cellular infiltration (lymphocytes and monocytes), coagulative necrosis with hemorrhage.

fell to 120/75 on the day after admission and then returned to its initial level and remained so until death. The blood chemistry was normal, the urine showed a trace of albumin. The white blood cells were 22,400, with 76% neutrophils. Sedimentation times: February 8, 42 mm./hr.; February 15, 80 mm./hr.; February 17, 62 mm./hr. Roentgen ray of the chest showed cardiac enlargement and pulmonary congestion.

Comment. The patient, a known hypertensive cardiac, experienced sudden severe choking as an equivalent of cardiac pain; this was followed by dyspnea and cardiac failure in which previous exertion did not play a rôle. Except for the absence of pain the patient presented many of the usual features of coronary thrombosis.

CASE 7.—H. P. (No. 1058), a 51-year-old white male factory worker, entered the hospital, October 28, 1936. One hour before admission, shortly after eating lunch, he suddenly experienced great weakness and faintness. He sat down in order to avoid falling. He felt nauseated and then vomited several times; profuse perspiration then developed. On admission he still complained of weakness, nausea and vertigo and stated that he "was frightened about himself." He was emphatic on the point that there had not been any pain in the chest, abdomen, neck, or arms and that he had never experienced abdominal or "hunger" pains. On rare occasions during the past few years he has had slight vertigo and mild exertion dyspnea. (Several days later on further inquiry he admitted that there had been occasional "heaviness" of the chest when he exerted himself extremely, but he had not given this any attention.) The past history was negative. His father died of a "stroke" and his mother of "acute indigestion."

The examination revealed a somewhat obese, well-developed white male who seemed apprehensive and who answered questions in a weak voice. Temperature, 97° F.; pulse, 120; respirations, 24. The face was pale and the lips cyanotic. The pupils were equal and reacted to light and accommodation. Blood pressure, 160/110. The left border of the heart was 3 cm. outside the nipple line; the heart sounds were fair in quality; no murmurs; the aortic second sound slightly accentuated. A few râles were noted at the right base. The abdomen was flat, no rigidity or masses; slight tenderness and slight resistance of the upper abdomen. The remainder of the examination was negative.

Perforated peripyloric ulcer or coronary thrombosis seemed to be the probable diagnosis. An electrocardiogram taken immediately revealed changes typical of anterior coronary occlusion (Fig. 5). The white blood cell count was 7800, the sedimentation time 17 mm./hr. One hour after admission the blood pressure was 130/95; 3 hours, 100/70; 5 hours, 100/70.

He was treated as a coronary thrombosis and by evening was quite comfortable except for gradually developing dyspnea and orthopnea. Slight nausea persisted. On the following day he vomited once. The weakness persisted, dyspnea and orthopnea diminished. Râles could be heard over both bases. Blood Wassermann test negative. A trace of sugar was found in the urine and this persisted for 3 days (the admission specimen was free from sugar). Blood sugar: 125 mg. per 100 cc.; November 3, blood sugar, 260; November 6, 220 mg. per 100 cc.

On the second day a friction rub was detected over the precordium. The white cells had increased to 18,250 and the sedimentation was now 38 mm./hr., temperature 101° F. and the blood pressure 112/72. There was gradual improvement except for vomiting when he ate more than a few mouthfuls of food. On November 3: temperature, 100° F.; pulse, 100; blood pressure, 130/90; white blood cells, 17,600; sedimentation, 90 mm./hr.

The basal râles persisted. The electrocardiogram of November 4 is shown in Figure 6. On November 7, no change was noted in the electrocardiogram. The sedimentation time was now 102 mm./hr. Early the morning of November 8 he mentioned mild aching in both shoulders. Two hours later he was found dead in bed. Except for this aching his history was devoid of pain. An autopsy could not be obtained.

Comment. This case was selected to illustrate the so-called "digestive group;" in this patient the symptoms resembled those encountered in an abdominal lesion, for example, atypical ruptured ulcer.

Since this paper is intended to emphasize some of the common clinical features of "painless" coronary artery disease, detailed comment upon the subject of cardiac pain is not relevant. However, attention may be momentarily directed toward one aspect of the pathologic physiology of the situation.

Unfortunately our past records are not sufficiently complete for ascertaining whether or not the cases reported belong to Libman's hyposensitive group. The existence of individuals hyposensitive to pain seems unquestionable. However, this theory was probably never intended to represent a complete explanation for absence of pain in coronary thrombosis. On the other hand, it is generally known that destruction of the vessels, nerves and functioning muscular tissue, renders an area insensitive so that painful responses are not experienced when new obstruction develops. For this reason it would seem reasonable to assume that in some cases the absence of pain in coronary artery disease could be explained upon the basis that the infarction occurs into a "dead" area. This seemed to have occurred in the third case reported. The microphotograph is taken from nearby areas of the myocardium (Fig. 7). The picture strongly suggests that the infarction occurred into a fibrotic area.*

The detailed description of the microscopic sections of Case 3 follows. It should be noted that the second paragraph of the description arises from other sections than those depicted here.

CASE 3 (Cont'd).—"Microscopic section of the heart shows a myocardial layer of varying thickness distorted by rather extensive chronic degenerative necrosing and productive changes. Large areas of cardiac muscle fibers are in advanced states of hyalin and granular coagulative necrosis. Throughout this necrotic tissue varying amounts of actively proliferating fibrocapillary tissue is seen. Focal areas of lymphocytic, plasma cell and mononuclear cell infiltration are common. Many of the large mononuclear cells have brownish pigment granules in their cytoplasm and are probably indicative of previous hemorrhage. Free masses of yellowish-brown pigment are also noted throughout the developing connective tissue. Subjacent to the necrotic endocardial tissue is a thick layer of proliferating fibrovascular tissue in which there are several large areas of coagulative

* We are indebted to Dr. Francis D. Speer for the description of the microscopic sections. The extracts from autopsy protocols in the above reported cases are available through the courtesy of Dr. Andrea Saecone.

and lytic necrosis with somewhat recent hemorrhage. A large fibrinocellular thrombus is attached to the necrotic endocardial tissues. A fragment of papillary muscle shows extensive muscular cytonecrosis and active fibrous tissue proliferation. In the fibrofatty subepicardial tissue there is one moderate sized transected coronary vessel in the media of which definite hyalin changes are seen.

"Another section shows a large branch of a coronary vessel with an irregularly thickened wall and a lumen reduced to about 30% of its normal size. The lumen contains a small amount of eosinophilic material and a few poorly preserved red cells. The lining endothelium is intact but shows small amounts of attached granular and fibrinous material. The intima is thickened and shows a variety of necrosing, fibrosing and calcific changes. An occasional distorted fragment of the internal elastic membrane can be identified. The muscular layer is very thin and shows poorly stained atrophic smooth muscle fibers. Throughout the myocardium of this section there is a fine fibrillar fibrosis often taking the form of small stellate shaped scars. Focal areas of muscular cytonecrosis are often in or near these fibrotic areas.

"Pathological Diagnoses. Advanced coronary atherosclerosis with calcification. Marked cardiac infarct showing advanced muscular necrosis and active organization with old and recent hemorrhage into the area of infarction. Intracardial fibrinocellular thrombosis."

The absence of pain in myocardial infarction has been explained by the assumption of the extravasation of blood into a fibrotic area. Stated in this manner, the explanation seems applicable in only 1 of the cases reported above. Further light has been thrown upon this question by animal experimentation, particularly by the work of Katz. If the nerve plexus surrounding a coronary vessel is destroyed by phenol, compression of the artery does not induce responses which are considered identical with pain; however, the response is not abolished when an area above the phenolized vessel is stimulated. The part played by the nerve plexus in coronary pain will be the subject of a future communication.

Summary. Additional evidence is submitted to support the idea that major coronary thrombosis may occur without pain. Pain was not present in one-third of 127 cases of coronary thrombosis observed by the writers during a 25-month period, although its occurrence was the subject of particular inquiry.

Seven cases of this type are reported briefly. The occurrence of 3 female cases among 7 reports is suggestive of the increasing occurrence of coronary thrombosis in women. Although Metropolitan Hospital has a large negro clientele, only 1 colored patient is reported and he was the son of a white father and half-white mother.

Most of the cases were known cardiacs and had manifested more or less cardiac failure for periods varying from a few weeks to many years. Sudden inexplicable increased congestive failure in a known cardiac should arouse suspicion of coronary thrombosis; moreover in such cases pain is usually absent. We had 1 case of a pain equivalent in the form of "choking," several of severe vertigo,

commonly associated with periods of unconsciousness, and 1 of a painless episode in the so-called "digestive" group.

The diagnosis of painless coronary thrombosis, as a rule, should not be difficult if the possibility is considered. Our mistakes have occurred mainly in elderly individuals with known arteriosclerotic heart disease and hypertension.

Painless coronary thrombosis probably occurs more frequently than is generally appreciated and we may assume that mild cases are more common than the fatal examples reported in this paper.

As the histories of these cases are singularly free from pain, they may belong to Libman's hyposensitive group. It is suggested that greater attention should be paid to the nerve plexuses surrounding the coronary vessels in cases of painless coronary infarction.

CEREBRAL EMBOLISM AS A COMPLICATION OF CORONARY THROMBOSIS.*

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LEVINE^{5a} has made the statement, "When a sudden hemiplegia occurs in a patient whose blood pressure is not remarkably elevated, the diagnosis of cerebral hemorrhage is too often made. In some cases of this type, the hemiplegia is due to an embolus and not to a hemorrhage and more careful search for data pointing to coronary thrombosis should be made." At even an earlier date, Cabot² had made similar remarks.

Interest in this subject was stimulated by the repeated emphasis of Levine^{5b} that emboli from cases of coronary thrombosis might explain some of the obscure hemiplegias and also because of observing at autopsy a case with an antemortem diagnosis of cerebral hemorrhage, which created no particular curiosity in itself, but later caused considerable excitement upon discovery of a rather extensive, unpresumed myocardial infarct with mural thrombi and the brain apparently the site of an embolus.

The literature failed to exhibit studies presenting the incidence of unsuspected coronary thrombosis in cases with a clinical diagnosis of either cerebral hemorrhage or cerebral thrombosis. Consequently, to determine the true incidence of cerebral embolism as a sequel of coronary thrombosis one must not concentrate attention wholly upon those cases known to have coronary thrombosis.

* Part of thesis which was submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Master of Medical Science (M.Sc.(Med.)) for graduate work in internal medicine. Presented (by invitation) before the Section on General Medicine of the College of Physicians of Philadelphia on May 24, 1937.

Analysis of 138 Consecutive Brain Examinations. Because of the observation that coronary thrombosis might be entirely unindicated in some of the hemiplegics, 1000 consecutive, unselected autopsies* were studied from the standpoint of the relationship between cerebral lesions and coronary thrombosis. Of the 1000 cases, there were 138 whose brains were examined at autopsy. Hemiplegia or hemiparesis was responsible for examination of the brain in 99 cases (on the left side in 46, on the right in 39, and bilateral in 4). Hemiparesis was reported on the left side in 9, and on the right side in 6.

TABLE 1.—THE INDICATION FOR BRAIN EXAMINATION.

Chief neurological sign or symptom leading to brain examination.	No. of cases.	% of the total.
Hemiplegia (recent)	65	47.1
Hemiplegia (old and recent)	15	10.8
Hemiplegia (became unconscious)	9	6.5
Hemiparesis	10	7.2
Weakness or paralysis of one or more extremity	10	7.2
Unconscious (sudden)	7	5.0
Severe headache	4	2.9
Aphasia	3	2.1
Dizziness	2	1.4
Blindness	2	1.4
Delirium	3	2.1
Skull fracture	1	0.7
Spastic quadriplegia	1	0.7
Bell's palsy	1	0.7
Meningismus	1	0.7
Sudden death after thoracocentesis	1	0.7
Change in personality	1	0.7
Became confused	2	1.4
Total	138	

TABLE 2.—CHIEF FINDING AT AUTOPSY.

	No. of cases.	% of the total.
Cerebral thrombosis	77	55.8
Cerebral hemorrhage	25	18.1
Thrombosis and hemorrhage	4	2.9
	106	
Meningitis (2 miliary abscess)	5	3.6
Marked cerebral arteriosclerosis	4	2.9
Subdural hemorrhage	3	2.1
Edema and congestion	3	2.1
Old cortical scars	2	1.4
Tuberculoma	2	1.4
Abscess	2	1.4
Glioma	2	1.4
Metastatic carcinoma	1	0.7
Fibroblastoma	1	0.7
Extradural hemorrhage	1	0.7
Cerebral atrophy (idiot)	1	0.7
Multiple sclerosis and old hemorrhage	1	0.7
Subarachnoid hemorrhage	1	0.7
Meningovascular syphilis	1	0.7
Cerebral thrombosis and myomalacia of cord	1	0.7
Embolism	1	
Total	138	

* From the files of the Phila. Gen. Hosp. Laboratories; acknowledgment is hereby made to the members of the laboratory staff for permission to use this material.

Table 2, which shows the chief pathologic lesion of each brain, reveals that cerebral thrombosis was present in 77, hemorrhage in 25, both thrombosis and hemorrhage in 4, and embolism in 1. The group comprised of thrombosis, hemorrhage, thrombosis and hemorrhage, and embolism accounted for 107 (77.5%) of the cerebral lesions. One is impressed with the scarcity of embolism but upon investigation it appears to be not a question of scarcity as much as difficulty in differentiating embolism from thrombosis. Dr. Riggs,^{8*} who examined practically all of these brains, thinks it possible that some of the cases listed under cerebral thrombosis may be cerebral embolism; however, in some instances she found it impossible to make the differentiation.

In addition to the above cases that had the brain examined at autopsy, there were 29 that had definite clinical evidence of a cerebral lesion, but unfortunately the brain was not examined at autopsy. These cases, presented in Table 3, were not included with

TABLE 3.—CLINICAL NEUROLOGICAL SIGN OR SYMPTOM.

	No. of cases.
Hemiplegia { Right, 9 Left, 10 }	19
Hemiparesis (right)	2
Unconscious (sudden)	2
Speech difficulty, 1 arm weak	1
One arm flaccid	1
Twitching right side of body	1
Paralysis left arm and leg	1
Meningeal irritation	2
Total	29

the original 138 that were specifically examined for cerebral lesion, because the clinical picture might strongly suggest a cerebral lesion and yet the autopsy might only show cerebral arteriosclerosis, or congestion and edema, as was the case in 7 of the 128 cases whose brains were actually autopsied.

A word is needed here on the use of the term coronary thrombosis. Boyd properly warns against employing the term coronary thrombosis synonymously with myocardial infarct, for he points out that the latter might be due to causes other than coronary thrombosis. Nevertheless, since the terms were often used interchangeably in the pathologic descriptions, they are similarly used here.

Analysis of Patients with Coronary Thrombosis. Of the 1000 cases studied, all had both gross and microscopic examination of the heart. In this group, there were 41 cases with established coronary thrombosis. Twelve of the 41 cases (29%) were associated with either cerebral thrombosis or cerebral embolism. These figures differ decidedly from those in the literature.

Conner and Holt,³ in reviewing 287 cases with coronary throm-

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bosis, state that 14 had developed cerebral embolism and 2 exemplified cerebral thrombosis many months after the attack of coronary thrombosis. In this series, approximately 5% of the patients with coronary thrombosis developed cerebral embolism.

TABLE 4.—ANALYSIS OF 41 PATIENTS WITH CORONARY THROMBOSIS.

	Age.			Sex.		Color.	
	20-39.	40-59.	60-79.	Female.	Male.	White.	Colored.
Coronary thrombosis and/or myocardial infarct*	5	21	15	16	25	25	16
Above cases complicated by cerebral thrombosis or cerebral embolism	3	5	4	2	10	10	2

* Of the 41 cases with coronary thrombosis, 4 occurred in syphilitic heart disease, 2 in rheumatic heart disease and the remainder in either arteriosclerotic heart disease or normal hearts.

Parkinson *et al.*⁷ refer to embolism as a complication of coronary thrombosis and of 83 cases autopsied, found cerebral embolism in 1 (an incidence 1.2%).

Meakins and Eakins⁶ report the autopsy findings of 62 cases with coronary occlusion and state that 6.4% had a cerebral thrombosis.

From the above studies, one readily observes that there is considerable variation in the occurrence of cerebral embolism in cases with coronary thrombosis. One will also notice a marked difference between the above reports and the present study. The 12 cases presented in this study having both a cerebral lesion and a coronary thrombosis had a clinical diagnosis of either cerebral hemorrhage or cerebral thrombosis. The cardiac lesion in all but 2 was unexpectedly found at autopsy. In these two exceptions the suspicion of coronary thrombosis was aroused, but the diagnosis was not definitely established. These cases would not have been discovered had they been studied from the aspect of cerebral embolism in cases with coronary thrombosis.

Of the 41 cases with coronary thrombosis, 29 had a clinical diagnosis corresponding to the pathologic finding. The additional 12 cases of coronary thrombosis were found indirectly by determining the incidence of unsuspected coronary thrombosis in cases with a clinical diagnosis of cerebral hemorrhage or cerebral thrombosis.

In Table 3, 29 cases are presented showing clinical evidence of a cerebral lesion, but the brain was not examined at autopsy. Two of these cases had coronary thrombosis which was also recognized clinically. From the latter group, wherein only the hearts were examined, one notes that the occurrence of associated cerebral embolism and coronary thrombosis is not as high as in the group where the brains as well as the hearts were examined at autopsy. Incidentally, the brains were not routinely examined in the studies reported by Connor and Holt,³ Parkinson *et al.*,⁷ and Meakins and Eakins.⁶ If we could feel justified in assuming that each of the 29 cases with neurologic manifestations but no brain examination had

a definite cerebral lesion of the nature of a thrombus or an embolus, then we could say that of the 29 cases with coronary thrombosis recognized clinically (from the group of 41) there were 2 (6.9%) that were complicated by either cerebral thrombosis or embolism. This latter figure would compare favorably with the reports of the above authors.

Coronary Thrombosis Often Unsuspected in Presence of Cerebral Lesion. While it appears that investigators are quite aware of cerebral embolism as a complication of coronary thrombosis, they are not so alert in recognizing the condition when the coronary thrombosis is not obvious and the first symptoms are those of embolism. Table 4 would also indicate that the white male of 40 or over is the most prone to develop cerebral embolism as a complication of coronary thrombosis.

If this high incidence of cerebral thrombosis or embolism in patients with coronary thrombosis can be substantiated, it seems that we have not been sufficiently aroused by the previously mentioned warning of Levine,^{5a} even though some of these cases were admitted to the neurologic service in stupor thereby making it impractical to obtain accurate information concerning previous history. Some of these cases had complained of either substernal pain, epigastric pain, arm pain, or neck pain 6 to 8 weeks prior to the onset of hemiplegia. These probably were some of the atypical forms of coronary thrombosis.

It is well known that one may have a painless coronary thrombosis. East *et al.*,⁴ as well as many others, have called attention to this fact. Parkinson⁷ says that dyspnea may replace and take the part of pain if infarction is superimposed on preëxisting signs of heart failure. Painless coronary thrombosis, as well as other atypical forms, might assist in explaining why the coronary thrombosis is not always suspected. It is also possible that cerebral thrombosis might be merely coincidental to the fall in blood pressure which frequently accompanies coronary thrombosis. The clinical picture of cerebral thrombosis thereby masking the cardiac lesion.

In the analysis of 138 brain examinations of which 12 cases (8.6%) also had coronary thrombosis, let it be recalled that the diagnosis of coronary thrombosis was not given in a single case and suspected in only 2. Excluding those cases whose brains showed glioma, fibroblastoma, tuberculoma, and so on and considering only those cerebral lesions which might have some relation to the events which follow coronary thrombosis (cerebral hemorrhage, cerebral thrombosis and cerebral embolism) we could then say that the incidence would be 12 out of 107 (11.2%) which had a cerebral thrombosis associated with coronary thrombosis. Analogous figures of other writers are not given because no similar studies were found.

A study is now being conducted to determine clinically the occur-

rence of coronary thrombosis in cases with a clinical picture of a cerebrovascular lesion.

Summary and Comment. One thousand consecutive, unselected autopsies were analyzed for the incidence of cerebral embolism and cerebral thrombosis in cases known to have coronary thrombosis. The same series was then analyzed for the incidence of unsuspected coronary thrombosis in cases with a clinical diagnosis of cerebral hemorrhage, cerebral thrombosis and cerebral embolism.

Of the 1000 cases, there were 138 whose brains were examined at autopsy. Of these, 107 had either cerebral hemorrhage, cerebral thrombosis or cerebral embolism. Of these 107 there were 12 cases (11.2%) that also had coronary thrombosis. The latter lesion was not diagnosed clinically in a single case and suspected in only 2.

While there were 41 cases of coronary thrombosis in the series of 1000 autopsies, only 29 of these were clinically recognized and recorded. The remaining 12 were found as clinically unsuspected coronary thromboses in the autopsy records of the 107 cases that had a clinical diagnosis of either cerebral hemorrhage, cerebral thrombosis or cerebral embolism. None of the 29 cases clinically recognized was shown to be associated with a cerebral lesion. The association of 12 of the 41 cases of coronary thrombosis with a cerebral vascular lesion gives an incidence of 29%, a higher figure than those found in the literature.

Though this series is too small to permit definite conclusions, this indication of a high incidence of unsuspected coronary thrombosis in cases of hemiplegia should serve as a stimulus for more extensive study and investigation.

As a result of the findings of this study, the following suggestions present themselves:

1. While it is generally felt that the heart is frequently the source of a cerebral embolus in persons below 40 years, it would be wise to suspect the heart in all cases of cerebral embolism, irrespective of the patient's age.

2. When suspecting the possibility of coronary thrombosis as the etiologic factor in a case of hemiplegia, we must bear in mind the atypical forms of coronary thrombosis and must not lose sight of the fact that in cases with congestive heart failure the coronary thrombosis might be masked by dyspnea.

3. All cases of hemiplegia should have a careful search made for any clue leading toward old or recent coronary thrombosis in addition to routine electrocardiographic tracings.

4. In order to establish the true incidence of cerebral embolism or cerebral thrombosis as a sequel of coronary thrombosis, we must examine the heart at autopsy in all cases that clinically have a cerebral lesion. Also we must examine the brain in all cases with coronary thrombosis that had any neurologic manifestations.

REFERENCES.

- (1.) Boyd, W.: Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1931.
 (2.) Cabot, R. C.: Facts on the Heart, Philadelphia, W. B. Saunders Company, 1926.
 (3.) Conner, L. A., and Holt, E.: Am. Heart J., 5, 705, 1930. (4.) East, C. F. T., Bain, C. W. C., and Cary, F. L.: Lancet, London, 2, 60, 1928. (5.) Levine, S. A.: (a) Coronary Thrombosis, Med. Mono., Baltimore, Williams & Wilkins Company, vol. 16, 1929; (b) Medicine, 8, 245, 1929. (6.) Meakins, J. C., and Eakins, W. W.: Canad. Med. Assn. J., 26, 23, 1932. (7.) Parkinson, J., and Bedford, D. E.: Lancet, 1, 4, 1928. (8.) Riggs, H. E.: Personal communication.

OBSERVATIONS ON THE THERAPEUTIC VALUE OF SULPHANILAMIDE IN BETA-HEMOLYTIC STREPTOCOCCUS PHARYNGITIS.

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DURING the past few years several reports of clinical and experimental studies of the chemotherapeutic effect of para-amino-benzene sulphanilamide and certain of its derivatives in beta-hemolytic streptococcus infections have appeared in the foreign literature, and more recently Long and Bliss,^{1a,b} and Marshall *et al.*² have made important contributions in this country. These studies have suggested that sulphanilamide may be of considerable benefit in the treatment of acute beta-hemolytic streptococcus infections, and convince one that these substances should receive further clinical trial. We have recently had the opportunity of evaluating its use in a series of 33 cases of beta-hemolytic streptococcus pharyngitis in a group of adolescents. In such a group this type of infection is important, not only because of its communicability but also because of the tendency for throat cultures to remain positive for a long period of time and consequently necessitate a long isolation period after apparent recovery from illness. Our interest in the use of sulphanilamide in these infections has been centered chiefly in determining whether or not its use might shorten the period during which throat cultures remain strongly positive. It is obvious that the throat culture is not an accurate quantitative method of determining the effect of any chemical on beta-hemolytic streptococci which have invaded the mucous membranes; but it is the only method applicable to this study and we feel that the frequency and care with which throat cultures were taken have somewhat reduced its unreliability. The rapidity of the absorption of sulphanilamide when given by mouth and its subsequent concentration in the blood and other body fluids has been investigated and it seems probable that it would inhibit the growth of bacteria in the mucous membrane of the pharynx.

Material. The 33 cases of beta-hemolytic streptococcus pharyngitis occurred in previously healthy young males ranging from 14 to 20 years. We have omitted data on a few other cases which either were not under

our care during their entire illness, or which developed some accompanying illness making their clinical course unsatisfactory for comparison.

In Table 1 are shown clinical data on the first 14 cases. Fever persisted from 2 to 7 days, 3 days being the most usual duration, and did not ordinarily exceed 102° F. There was leukocytosis in all cases ranging from 10,500 to 23,700 white blood cells per c.mm. At no time was there any evidence that the infection was milk-borne or carried by food handlers. In one column the initials of the individual who had contact with that patient before the onset of his illness are given; these data seem to indicate that the epidemic was definitely of the contact type. No definite history of exposure to other members of the group could be obtained from two individuals. Similar clinical data on the next 19 cases are given in Table 4; their clinical courses seemed essentially the same as those of the members of the first group.

TABLE 1.—CLINICAL DATA ON THE FIRST 14 CASES.

Name.	W.B.C. on adm. (thous.)	Days of fever.	Highest temperature.	Date admitted.	Contact.
A. W.	17.9	3	103.5	2-5	First case
D. J.	16.6	5	102	2-6	A. W.
J. F.	15.3	2	100	2-7	D. J.
J. E.	13.9	7	101.5	2-8	J. F.
F. C.	13.8	3	101.8	2-8	?
D. K.	10.5	2	101.8	2-8	D. J.
T. C.	18.4	3	101.6	2-9	F. C.
S. W.	23.7	3	101.5	2-10	D. K.
A. H.	20.3	2	101	2-11	F. C.
R. A.	18.2	3	102	2-12	A. H.
L. B.	14.6	2	101	2-14	A. H.
R. B.	13.9	4	101.5	2-15	L. B.
W. M.	15.5	2	102	2-15	?
B. J.	14.2	2	102.2	2-16	R. B.

Procedure. At the beginning of the outbreak it was felt desirable to withhold specific treatment from 10 individuals for about 10 days, so that we could determine whether the throat cultures would remain strongly positive for at least that length of time. The data in Table 2 show that 12 of the 14 patients had strongly positive throat cultures for more than 10 days. In the first group, 6 cases were given 40 grains of sulphanilamide daily (approximately 0.5 gm. per 10 kilos of body weight), in 4 equally divided doses beginning not earlier than the 11th day; 4 patients received 100 grains of sulphanilamide daily (approximately 1 gm. per 10 kilos of body weight), beginning not earlier than the 14th day; and 4 were given 40 grains daily beginning on the second or third day of illness. These 14 cases gave us an opportunity to determine about how long we might expect cultures to remain positive and an opportunity to develop some familiarity with the therapeutic agent.

Table 3 gives data on the next 19 cases. Eight of these patients were given daily doses of sulphanilamide equivalent to 1 gm. per 10 kilos of body weight, starting on from the 4th to the 6th day of the disease. The other 11 cases were given similar doses of sulphanilamide but therapy was begun not later than the 3d day of the disease. In addition to specific therapy each patient was given only such usual treatment as forced fluids, and frequent hot saline throat irrigations. Throat cultures were taken almost daily and were streaked on blood agar plates without delay.

A practically pure culture of beta-hemolytic streptococcus has been recorded as +++, a marked predominance ++ and the presence of a few colonies +.

TABLE 2.—DATA ON THROAT CULTURES AND SULPHANILAMIDE THERAPY FOR THE FIRST 14 CASES.

Name.	Day sulphanil- amide started	Number of days given.	Daily amount (grams)	Day of disease.													
				1	2	3	4	5	6	7	8	9	10	11	12	13	14
A. W.	12	5	40	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
D. J.	13	5	40	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
J. F.	12	5	40	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
J. E.	12	8	40	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
F. C.	11	6	40	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
D. K.	10	6	40	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
B. J.	2	7	40	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
W. M.	3	8*	40*	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
R. B.	3	9†	40†	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
L. B.	3	8†	40†	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
R. A.	14	4	100	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
J. H.	16	3	100	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
S. W.	16	3	100	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
T. C.	14	8	100	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++

* Sulphanilamide 100 gr. daily starting 11th day for 6 days.

† Sulphanilamide 100 gr. daily starting 12th day for 4 days; transferred for care elsewhere on 16th day.

† Sulphanilamide 100 gr. daily starting 13th day for 3 days.

TABLE 3.—DATA ON THROAT CULTURES AND SULPHANILAMIDE THERAPY FOR THE GROUP OF 19 CASES.

Name.	Day sulphanil- amide started	Number of days given.	Daily amount (grams).	Day of disease.														
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
G. I.	6-12*	33*	100	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
P. B.	4	3	100	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
J. O. B.	6	5	100	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
J. G.	5	5	100	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
R. O.	5	4	120	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
J. W.	5	5	120	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
O. B.	4	5	90	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
S. D.	4	5	75	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
S. B.	2	10	90	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
D. P.	2	10	100	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
G. P.	2	6	90	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
J. McL.	3	5	90	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
C. H.	3	5	120	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
W. S.	2	5	90	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
J. L.	2	5	100	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
J. P.	1	4	90	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
J. A.	2	4	90	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
T. B.	2	4	100	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++

* Interval of 3 days without sulphanilamide.

† To 25th day + + +, then transferred elsewhere for further care.

The streptococci were isolated in pure culture from 12 patients. These 12 strains were then incubated at 37° C for 17 hours in blood broth, 0.1 cc. of this growth was added to 5 cc. of blood broth, and after 7 hours incubation dilutions of 10^{-1} , 10^{-2} , 10^{-3} , 10^{-4} , 10^{-5} , and 10^{-6} were made in nutrient broth. One cc. of these dilutions was inoculated intraperitoneally in mice, and at death cultures were made from heart's blood and peritoneal exudate. No mice died within 7 days when the dilution was greater than 10^{-1} .

Results. In the first group of 14 patients, members of which were given only small doses of sulphanilamide or larger doses very late in the disease, the throat cultures remained positive for 12 days or more in 13 patients and for 16 days or more in 6 patients; 5 of the 6 patients who were given small doses of sulphanilamide late in their disease showed negative throat cultures almost directly, but it seems unlikely that the treatment was responsible for this result. It seems more probable that these throat cultures would have become negative at that time if no treatment had been given. Similar results followed the use of larger doses of sulphanilamide late in the illness of 4 patients; but it is difficult to believe that the drug could have effected a change so rapidly. Four patients received small daily doses of sulphanilamide starting early in their disease, and in only one instance was the period of positive throat cultures definitely shortened. The data obtained in this group indicate the length of time during which throat cultures tend to remain positive for beta-hemolytic streptococcus in this type of illness and is important for comparison with the second group of patients. Data in Table 3 indicate that different results were obtained when larger doses of sulphanilamide were given early in the disease (clinical data concerning this group are given in Table 4). In this group of 19 patients only 6 patients had a positive throat culture on the 12th day, in contrast with 13 out of 14 patients in the other group. Only 3 of the 19 had positive cultures on the 16th day, in contrast to 6 patients out of 14 patients in the other group. In the first group only 1 patient out of 14 had a negative throat culture on the 5th day of his illness, while in this group 6 out of 19 patients had negative cultures on that day. The number of patients in the two sections of this group, *i. e.*, those who were given sulphanilamide on or before the 3d day and those who started treatment from the 4th to the 6th day, is too small to permit one to draw definite conclusions; but it does not appear that this degree of delay in starting therapy affected the results; however, there does not seem to be any advantage in delaying the therapy. In this group of 19 patients there were 5 who seemed to have received little or no benefit from the sulphanilamide; there was nothing in their past histories nor any peculiarity in their upper respiratory tracts nor in the course of their illnesses which was noticeably different from that of other members of the group. It seems much more likely that these individuals were infected with a strain which is not affected by sulphanilamide; but it is possible that these

patients either absorbed the drug very poorly or excreted it very rapidly. There can be little doubt in the mind of anyone who has worked with even such a small group of patients as this that, in a significant proportion of individuals who have been infected with certain strains of beta-hemolytic streptococcus, sulphanilamide will inhibit the growth of the bacteria. The strains isolated from these patients were of low virulence for mice as were those strains isolated from several other patients.

TABLE 4.—CLINICAL DATA ON THE GROUP OF 19 CASES SIMILAR TO THAT GIVEN IN TABLE 1 FOR THE FIRST 14 CASES, AND IN ADDITION DATA ON THE TOXIC SYMPTOMS WHICH DEVELOPED.

Name.	Days fever.	Highest temperature.	W.B.C. on adm. (thous)	Day sulphanilamide started.	Day headache.	Day rash.	Day cyanosis.	Day abdo. cramps.
G. I.	3	100	11.0	6	7	..	15	
P. B.	3	100	13.0	4	6	..		6
J. O.	2	100.8	19.6	6				
J. G.	2	100.2	14.6	5	..	13		
R. O.	2	101.8	16.2	5	7	..	8	
J. W.	1	100	17.7	5	..	12	8	
O. B.	2	99.6	14.7	4				
S. D.	3	102	18.2	5	7			
S. B.	2	102	16.2	2	3			4
D. P.	3	102	12.9	2	3	12	11	
G. P.	2	101.5	19.8	2	3	11	10	
J. M.	2	100.5	13.8	2	3			
C. H.	2	99.8	10.0	3	..	10	..	9
W. D.	2	102.8	12.8	3				
W. S.	2	102	11.7	2	5	
J. L.	2	100	15.7	1				
H. P.	2	101.8	14.8	2	4	
J. A.	3	102.8	14.6	2	7	..	5	
T. B.	2	102.5	14.6	2	5	

Toxic Effects. In the course of this study we have observed certain toxic effects of sulphanilamide (Table 4). No toxic effects were observed in the patients who received only 40 grains of sulphanilamide daily; 2 patients in the first group who received 100 grains became slightly cyanosed, but there were no other significant manifestations of toxicity in that group. Of the 19 patients who received about 1 gm. per 10 kilos of body weight daily, 9 developed headache accompanied by slight elevation in temperature on from the 2d to the 4th day after therapy was begun; and 9 became moderately cyanosed from the 4th to the 10th day of treatment. The precaution of not using saline laxatives has been advised and none of these patients received such medication. Three individuals complained of abdominal cramplike pain, which may have been caused by the sulphanilamide. Five patients developed a morbilliform type of rash which was widely distributed over the arms, neck and chest; this rash appeared on from the 10th to the 13th day after the therapy was begun, caused little discomfort, and disappeared within 3 or 4 days.

Summary. 1. Observations on the value of sulphanilamide in 33 cases of pharyngitis caused by strains of beta-hemolytic streptococcus of low virulence for mice are reported.

2. The administration of doses of sulphanilamide in amounts equivalent to 1 gm. of sulphanilamide per 10 kilos of body weight daily early in the course of these cases of beta-hemolytic streptococcus pharyngitis apparently shortened the length of time during which throat cultures continued to be positive for those bacteria in a significant proportion of cases.

3. The results obtained in this study suggest that small doses of sulphanilamide given early in such an illness are usually without demonstrable effect. When small or large doses are given late in such an illness, it is impossible to be certain that subsequent throat cultures have become negative because of the specific therapy.

4. The use of sulphanilamide in adequate dosage frequently produced mild toxic symptoms, such as headache, cyanosis and a morbilliform dermatitis; none of these manifestations were followed by serious consequences.

REFERENCES.

- (1.) Long, P. H., and Bliss, E. A.: (a) J. Am. Med. Assn., 108, 32, 1937; (b) Arch. Surg., 34, 351, 1937. (2.) Marshall, E. K., Emerson, K., and Cutting, W. C.: J. Am. Med. Assn., 108, 953, 1937.

THE INACTIVATION OF ESTROGEN BY THE LIVER.

OBSERVATIONS ON THE FATE OF ESTROGEN IN HEART-LUNG AND HEART-LUNG-LIVER PERFUSION SYSTEMS.*

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DESPITE the rapid progress, during the last decade, in the isolation, purification, and synthesis of the estrogens, their clinical dosimetry remains largely empiric. This is frequently the case with newly introduced therapeutic agents of low toxicity. However, when the clinical effects of a new agent are better understood, interest then centers upon a more exact administration of the sub-

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stance. This must in fact depend on a knowledge of the rate of utilization and the disposal level of the substance when administered in known quantities. The renal threshold for estrogen has been a subject of considerable study ever since Loewe and Lange¹ demonstrated its presence in the urine of normal women. Through the work of many investigators² we now know the urinary and fecal levels of estrogenic substance in health and disease. However, it has been apparent that the rate of disappearance of estrogens in the body varied under different physiologic and pathologic circumstances, and a knowledge of these variations has become essential for evaluation of the proper dosage.

Recently, many studies have been carried out in both animals and man in the hope of determining the fate of estrogens in the body under normal and abnormal conditions. These experiments have shown that most of the estrogen administered is not excreted, at least, not in a form recognizable by our present-day methods of detection. The total quantity of estrogen excreted, following oral or hypodermic administration to amenorrheic,³ pregnant,⁴ menopausal,^{5,6} or castrated⁷ women, and to males,⁴ has been shown to be no more than 20% of the amount administered. The actual amounts recovered varied from 3 to 20%, depending upon whether the fecal and urinary excretion was determined, and whether a hydrolysis technique of extraction⁸ was used. It was also observed^{3,4,5,7} that the maximum excretion of the estrogenic substance occurred within the first 24 hours of its administration, and that the excretion ceased after from 48^{4,5} to 96 hours,⁷ irrespective of the quantity administered. These observations on the speed with which administered estrogen is excreted are in agreement with the experimental data of McClendon, Burr and Conklin.⁹ Thus, while all observers agree that only a small portion of administered estrogen is eliminated as such from the body, there is no unanimity of opinion concerning the fate of the remainder.

Several investigators have attempted to determine the nature and site of the destruction of the estrogens, and the speed with which this occurs. Frank, Goldberger and Spielman¹⁰ have shown that estrogen, administered intravenously or subcutaneously in doses of from 2000 to 3000 mouse units to isolated female rabbits, disappears from the blood after 30 minutes and is not recovered from any of the organs extracted 24 hours after injection, except for small traces in the liver. A similar experiment in monkeys showed that only 20% of administered estrogen was excreted by the kidneys. These investigators concluded that the remainder of the estrogen was not stored in the body, but was either rapidly destroyed, or altered. Silberstein, Molnar and Engel,¹¹ working with the blood and liver of healthy male dogs, showed that both tissues, either together or separately, destroyed estrogen *in vitro*. They also demonstrated the degree and speed of estrogen destruction in

incubated dog blood to be 50% in 10 minutes, 80% in 30 minutes, and 96% in 120 minutes. The ability of liver tissue to destroy estrogen *in vitro* has been observed by others, but the efficacy of blood in this regard has not been corroborated. Fee, Marrian and Parkes,¹² employing the isolated heart-lung-kidney preparation of Starling and Verney,¹³ showed that only 1% of the total amount of estrogen introduced into the artificial circulatory system was excreted by the kidney. They also noted that the estrogen disappeared from the circulating blood of the artificial system within 25 minutes, only traces remaining in the heart, lungs and kidneys at the conclusion of the experiment. Their control mixtures of blood and estrogen, incubated at either 37° C. or at room temperature for 3 hours, showed no loss of estrogenic activity. Observing that estrogen rapidly disappeared from a heart-lung-kidney perfusion system and yet was not excreted by the kidney, destroyed by the blood, or stored in the organs, Fee, Marrian and Parkes postulated that the loss may be effected by an oxidation process in the pulmonary circulation.

Zondek,¹⁴ having found that rodents excrete none and humans only 3% of administered estrogen, attempted to discover the fate of the "retained" estrogen by extracting and assaying the finely-ground bodies of rodents at from 3 to 72 hours after the injection of estrogen. He recovered less than 1% of the injected estrogen by ordinary, neutral, extraction, but recovered larger amounts by an hydrolysis, acid-boiling, technique. Employing the latter method, Zondek recovered 20% of the estrogen after 24 hours, 6% at 48 hours and 1% at 72 hours. Concluding that estrogen administered to rats is neither stored nor excreted, and that it is either chemically altered or completely destroyed, Zondek sought the site of the change by determining the loss of estrogenic potency occurring in incubated mixtures of estrogen and various rodent organs. Of all the organs, only the liver showed a consistent effect on the added estrogen. In 5 of 7 experiments, the liver-estrogen mixtures showed more than 90% loss of estrogenic potency in 5 hours, whether or not acid hydrolysis was performed. More interesting are Zondek's further observations that, although aqueous and dried liver extracts would inactivate estrogen, boiled liver would not do so. On the basis of these *in vitro* experiments, Zondek postulated the existence of an hepatic enzyme, "œstrinase," capable of inactivating estrogens. Further indication that the liver may have a rôle in the metabolism of estrogens is found in the recent work of Rondoni, Carminati and Corbellini,¹⁵ who described the formation of an estrogenic substance by the interaction of cholesterol and liver tissue *in vitro*.

Although the experimental data cited indicate that the major portion of administered estrogen is altered in the body and further suggest that the liver effects the change, there is no unanimity of opinion concerning either the nature or the site of the process.

Our experiments were planned in an attempt to resolve the contradictory evidence^{11,12,14} concerning the effect of mammalian blood on estrogenic potency and to evaluate the possible existence of an hepatic "œstrinase."¹⁴ Believing that *in vitro* experiments which employ isolated tissues and invite a rich bacterial invasion are open to criticism, we sought a more physiologic experimental technique. Thus, in order to determine the effects of blood,^{11,12,14} lungs,¹² and liver¹⁴ on estrogen under similar conditions, perfusion experiments were chosen. It was thought that studies showing the comparative rates of disappearance of estrogen from mammalian blood *in vitro* and from mammalian blood circulating in heart-lung and heart-lung-liver preparations would be of crucial import. Perfusion experiments of the isolated liver¹⁶ are not entirely satisfactory. We therefore used the heart-lung preparation of Knowlton and Starling¹⁷ as a perfusing motor. Such heart-lung-liver preparations have been previously employed in studies of the detoxification of strychnine,¹⁸ quinidin¹⁹ and ouabain.²⁰ This technique, properly executed, affords adequate perfusion and maintains the functioning state of the liver, as is evidenced by the previous reports,^{18,19,20} and by our own observations which included histologic study of the perfused liver at the conclusion of the experiment (Figs. 1 and 2).

Perfusion Experiments. The apparatus used in the perfusion experiments was essentially the same as that employed by previous workers.^{18,19,20}

Two types of experiment were done. In the first series, the fate of a known amount of estrogen* introduced into heart-lung preparations was studied; and in the second series, the same objective was sought in heart-lung-liver preparations. This was accomplished by introducing into the circulation of a stabilized perfusion system known amounts of estrogen and withdrawing blood samples for estrogen-assay at intervals. Each experiment continued for at least 1 hour, a minimum of 4 blood samples being obtained. At the end of each experiment, the heart, lungs and liver were separately assayed for estrogen after alcohol extraction in a Soxhlet apparatus for 24 hours.

The experiments were performed in an identical manner. The dogs employed were anesthetized by sodium amytal (50 mg. per kilogram of body weight). In each experiment, the control specimens for estrogen-assay consisted of: 1, 30 cc. of perfusion blood removed from the system prior to the addition of estrogen (blood control); 2, a similar quantity of perfusion blood to which a known amount of

* The estrogen employed throughout these experiments was crystalline alpha-ketohydroxyestrin ($C_{18}H_{22}O_2$). One milligram of this crystalline substance is equivalent to 900 rat units in bio-assay. Prior to each experiment, 2 milligrams of the crystals (1800 rat units) were dissolved in 180 cc. of phosphate buffer (pH 7.9), bio-assayed, and employed as the stock solution for that one experiment. (The estrogen was supplied through the courtesy of Dr. Erwin Schwenk of the Schering Corporation.)

estrogen was added (blood-estrogen control); and, 3, a sample of the estrogen solution employed. The control specimens and the samples of blood withdrawn during the experiments were dried with anhydrous sodium sulphate, extracted for estrogen by the method of Frank and Goldberger²¹ and assayed on castrated adult rats (Allen and Doisy²²). The test rats employed in the assays weighed from 140 to 160 gm. Following castration, vaginal smears were examined daily for a minimum of 2 weeks to insure the presence of continuous anestrus. Each rat was then tested for sensitivity, and only those animals showing vaginal estrus in response to 1 rat unit of estrogen were used. From 16 to 30 rats were used in each assay. In the actual experiments we considered a positive reading to be the presence of estrus (vaginal smear technique) in both of the two rats employed in the final reading of each assay. The rats employed in those assays which yielded zero readings (less than 2 rat units) were retested for sensitivity with standard estrogen to insure the validity of these findings.

A protocol, typical of each perfusion experiment, is presented below.

TABLE 1.—DATA OF A HEART-LUNG PERFUSION EXPERIMENT, SHOWING THE NON-INACTIVATION OF ESTROGEN.*

Blood specimen number.	Minutes after introduction of estrogen.*	Estrogen content of 30 cc. blood specimen in rat units.
1	15	15
2	30	30
3	45	20
4	60	15

CONTROL AND TISSUE ASSAYS.

	Estrogen content in rat units.
Blood Control: 30 cc. of perfusion fluid removed prior to introduction of estrogen	less than 2
Blood-estrogen Control: 30 cc. of perfusion fluid plus 30 rat units of estrogen	30
Heart (at conclusion of experiment)	96
Lungs (at conclusion of experiment)	72

* 1000 rat units of estrogen added to approximately 1270 cc. of circulating perfusion fluid.

Protocols. *Heart-lung Perfusion (Table 1).* A heart-lung preparation was established in a dog weighing 8.6 kilograms, from which 200 cc. of blood had been previously taken. This blood and an additional 770 cc. of blood obtained from two other dogs were defibrinated, heparinized and introduced into the circuit of the preparation. A small amount of heparin was added to the blood circulating in the perfusion system to safeguard further against coagulation. The pressure of the circulatory system was appropriately regulated throughout the experiment. The perfusion circulation being well stabilized, 60 cc. of blood were removed at 12.15 P.M. Of this amount, 30 cc. were incubated at 37° C. for the duration of the experiment and then titrated for estrogen (blood control, Table 1). The remaining 30 cc., to which were added 30 rat units of estrogen in buffered solution, were likewise incubated and subsequently assayed (blood-estrogen control, Table 1). Immediately following the obtaining of the blood (60 cc.) for control analysis

at 12.20 P.M., 1000 rat units of estrogen in 100 cc. of buffered solution were introduced into the perfusion system. During the next hour 30 cc. specimens of blood were removed for bio-assay at each 15-minute interval. At the termination of the experiment, the heart-lung preparation was actively functioning. The heart and lungs were removed, extracted and assayed for estrogen.

TABLE 2.—DATA OF A HEART-LUNG-LIVER PERFUSION EXPERIMENT, SHOWING THE INACTIVATION OF ESTROGEN.*

Blood specimen number.	Minutes after introduction of estrogen.*	Estrogen content of 30 cc. blood specimen in rat units.
1	15	Less than 2
2	30	Less than 2
3	45	Less than 2
4	60	Less than 2
5	75	Less than 2
6	105	Less than 2

CONTROL AND TISSUE ASSAYS.

	Estrogen content in rat units.
Blood Control: 30 cc. of perfusion fluid removed prior to introduction of estrogen	Less than 2
Blood-estrogen Control: 30 cc. of perfusion fluid plus 30 rat units of estrogen	30
He (at conclusion of experiment)	4
Lu (at conclusion of experiment)	40
Li (at conclusion of experiment)	20

* 7 rat units of estrogen added to approximately 870 cc. of circulating perfusion fluid

Heart-lung-liver Perfusion (Table 2). A heart-lung circuit was established in a dog weighing 6 kg. and 670 cc. of blood obtained from two other dogs were collected, heparinized and added to the system's reservoir. At 10.25 A.M., less than 3 minutes of its excision, the liver of a healthy dog weighing 3.5 kg. was joined to the heart-lung circuit by the usual technique. At 10.40 A.M., the control 60 cc. of blood were removed from the circulation. Of these 60 cc., 30 cc. were incubated at 37° C. for the duration of the experiment and then titrated for estrogen (blood control, Table 2). The remaining 30 cc., to which were added 30 rat units of estrogen in buffered solution, were likewise incubated and subsequently assayed (blood-estrogen control, Table 2). Immediately after withdrawal of the controls, at 10.45 A.M., 1000 rat units of estrogen in 100 cc. of buffered solution were introduced into the perfusion circulation. Thereafter, at 15-minute intervals from 11 A.M. to noon, and 12.30 P.M.—30 cc. specimens of blood were removed for estrogen titration. Adequate heart action and liver circulation were maintained throughout the experiment. At the end of the experiment, the heart, lungs and liver were removed, separately extracted and assayed for estrogen.

Discussion. Strikingly uniform results were obtained in each series of experiments. It was shown that no destruction of estrogen occurs in canine blood *in vitro* (blood estrogen controls, Tables 1 and 2). These observations are not in agreement with those of Silberstein,¹¹ but are in agreement with those of other workers.^{12,14} Similarly, the estrogen concentration remained unaltered in the heart-lung perfusion experiments. The amount of estrogen in the

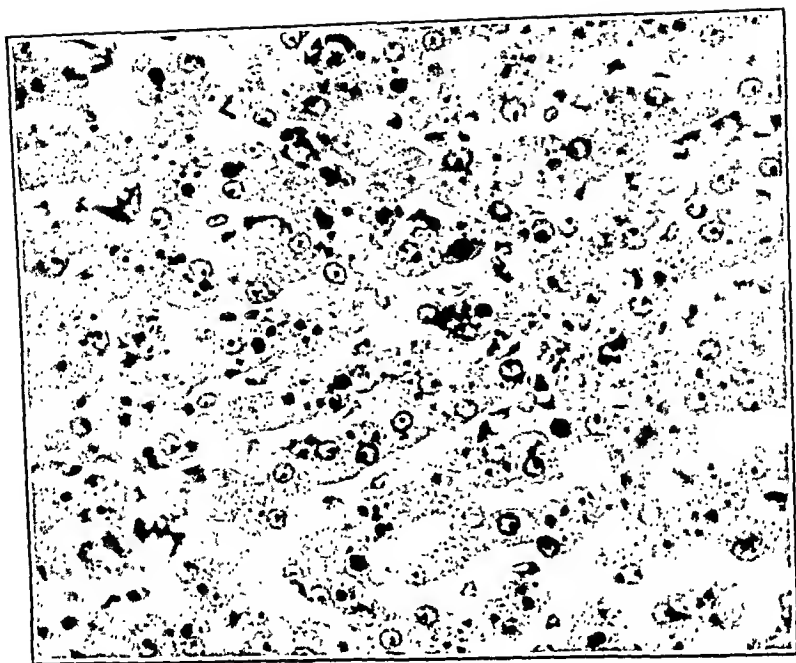


FIG. 1.—Photomicrograph of dog liver at the conclusion of heart-lung-liver perfusion experiment, showing slight cloudy swelling. ($\times 500$.)

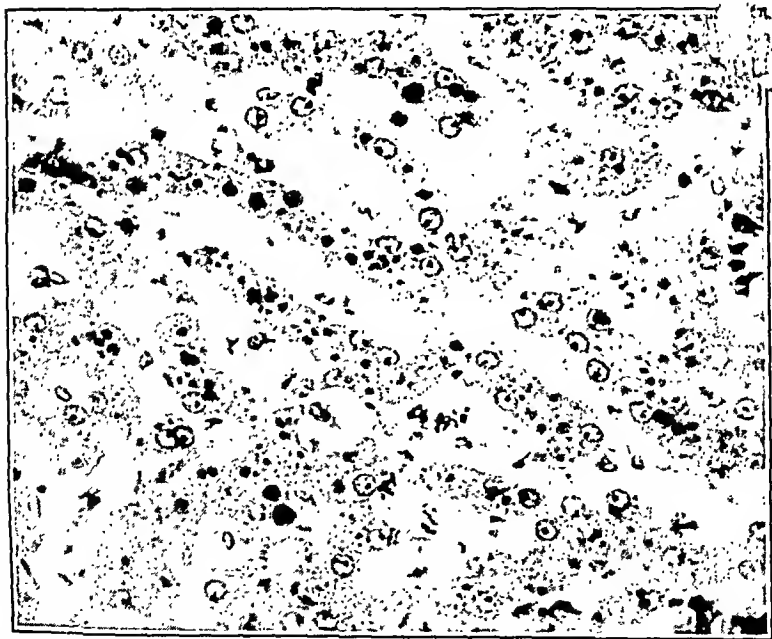


FIG. 2.—Photomicrograph of dog liver at the conclusion of heart-lung-liver perfusion experiment, showing moderate cloudy swelling and dilated sinusoids. ($\times 500$.)

30 cc. samples of blood, removed every 15 minutes throughout each of the heart-lung experiments, remained essentially the same (Experiments I and II, Table 3). It may be objected, in regard to the heart-lung perfusion experiments, that a partial loss of estrogen occurred within the first 15 minutes and that the amounts of estrogen recovered subsequently represented equilibrium conditions. We do not believe that this objection is a valid one. Estimating the total amount of fluid which circulated in one of the heart-lung experiments to be 1270 cc. (200 cc. remaining in the dog's heart-lung circuit, 970 cc. of defibrinated blood added to the system, and 100 cc. of estrogen solution containing 1000 rat units), the control concentration of estrogen approximated 0.8 rat units per cc. This concentration of estrogen remained practically stationary throughout the experiment (Experiment I, Table 3), indicating that no loss of estrogen occurred. This does not imply that the amount of circulating fluid remained constant throughout the experiment. Actually, a certain loss of fluid-volume inevitably occurs in all perfusion experiments because of unavoidable leakage. This is illustrated by the data of the same heart-lung experiment (Experiment I, Table 3), wherein the initial level of circulating fluid was 1270 cc. and the final level, as measured by air-irrigation and drainage of the system, equalled 850 cc. There is no reason to suppose, however, more especially since the estrogen is added in a perfectly admixed aqueous solution, that the lost blood is selectively deprived of its estrogen content as it leaks from the circuit. Our findings are not in accord with those of Fee, Marrian, and Parkes,¹² who postulated that estrogen is lost by pulmonary oxidation in a heart-lung perfusion system. The data of our heart-lung perfusion experiments force us to conclude that no loss of estrogen occurs in such a system.

TABLE 3.—DATA OF HEART-LUNG AND HEART-LUNG-LIVER PERFUSION EXPERIMENTS, SHOWING THE FATE OF ESTROGEN.*

Blood specimen (30 cc.).	Estrogen content in rat units.				
	Heart-lung.		Heart-lung-liver.		
	Exper. I.	Exper. II.	Exper. III.	Exper. IV.	Exper. V.
15 min.	15	15	Less than 2	Less than 2	10
30 min.	30	30	Less than 2	Less than 2	5
45 min.	20	30	Less than 2	Less than 2	Less than 2
60 min.	15	30	Less than 2	Less than 2	Less than 2
75 min.			Less than 2	Less than 2	Less than 2
105 min.			Less than 2	Less than 2	Less than 2
Organs at end of experiment.					
Heart	96	90	4		10
Lungs	72	90	40	30	99
Liver			20	45	60

* 1000 rat units of estrogen added to perfusion fluids which varied from 870 cc. to 1270 cc. in volume.

The results of the heart-lung-liver perfusion experiments are in striking contrast to the above-described observations (Table 3). Estrogen was rapidly and completely removed from the circulation in each of the 3 heart-lung-liver perfusion experiments. With a single exception this removal was complete within 15 minutes. This disappearance of estrogen represents, we believe, an actual inactivation of the substance, and may be seen from the final analyses of the organs perfused (heart, lungs and liver). It is noteworthy that the amounts of estrogen found in the heart and lungs of the heart-lung-liver perfusion experiments were, with a single exception, less than those found in the corresponding organs of the heart-lung experiments. This is further evidence that the final concentrations of estrogen circulating in the heart-lung-liver systems were definitely lower than those in the heart-lung circuits. Of even greater interest was the low content of estrogen in the liver, an organ weighing more than the combined weights of the corresponding heart and lungs. These data, corroborative of Zondek's¹⁴ *in vitro* experiments, suggest but in no wise prove the existence of an hepatic "œstrinase." The recent work of Cohen and Marrian,²³ showing that estrogenic substance is found in the urine of pregnant women in the form of a glucuronate ("œstriol glucuronic acid"), is of interest. Inasmuch as glucuronic acid is synthesized in the liver, the findings of Cohen and Marrian strengthen the link between the liver and the process of estrogen alteration. Whatever the mechanism by which the change is effected, it does appear that the liver in some manner inactivates estrogen.

That the liver of such a perfusion circuit is capable of performing many of its ordinary functions has been demonstrated by previous workers.^{18,19,20} The liver retained its normal color throughout each experiment. Gross evidence of edema did not appear. The hepatic blood flow remained continuous, and no areas of rupture or intrahepatic hemorrhage were noted. The blood entering the liver was red and that leaving it was such as to suggest that in its passage through the liver, oxygen utilization by the liver cells occurred. The photomicrographs of portions of two livers, prepared at the end of 2 experiments, show only the congestion and cloudy swelling anticipated from the conditions of the perfusion system (Figs. 1 and 2).

It is not surprising that so much estrogen is removed from the circulation of a heart-lung-liver preparation within the short time of 15 minutes. In the *in vivo* experiments of Frank, Goldberger and Spielman¹⁰ estrogen was not found in the circulation after 30 minutes. Priestley, Markowitz and Mann¹⁸ demonstrated, in heart-lung-liver perfusion experiments with strychnine, a concentration of the substance in the liver seven times greater than that in the circulating blood within 10 minutes. Similarly, a 50% decrease in concentra-

tion of circulating quinidin occurred within 13 minutes.¹⁹ Though the conditions are not precisely parallel, it may be noted that the dyes (bromsulphalein, etc.) employed in certain liver function tests disappear normally from the circulating blood within 30 minutes.

Summary. 1. A review of the current concepts of the fate of estrogen administered to animals and human beings is presented. It appears that only from 3 to 20% of administered estrogen is excreted, the remainder being irrecoverable in analyses of body organs.

2. In an attempt to resolve the controversial views concerning the fate of the "lost" 80% of administered estrogen and to evaluate the rôle of the liver in this process, the comparative rates of disappearance of known amounts of estrogen from standing dog blood and from dog blood circulating in heart-lung and heart-lung-liver perfusion preparations were determined.

3. These experiments show that estrogen is not inactivated by dog blood *in vitro* or by the circulation in a heart-lung perfusion system. It is rapidly inactivated by circulation in a heart-lung-liver perfusion system.

4. From these observations, it is concluded that the liver, in some manner, either destroys or alters circulating estrogen.

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REFERENCES.

- (1.) Loewe, S., and Lange, F.: *Klin. Wehnschr.*, 5, 1038, 1926. (2.) Dohrn, M., and Faure, W.: *Ibid.*, 7, 943, 1928; Luchsinger, J., and Voss, H. E.: *Ibid.*, 8, 1577, 1929; Siebke, H., and Schuschania, P.: *Zentralbl. f. Gynäk.*, 54, 1734, 1930; Smith, G. van S., and Smith, O. W.: *Am. J. Physiol.*, 100, 553, 1932; Kürzrok, R., and Ratner, S.: *Am. J. Obst. and Gynec.*, 23, 689, 1932; Frank, R. T.: *J. Am. Med. Assn.*, 104, 1991, 1935; Cohen, S. L., Marrian, G. F., and Watson, M.: *Lancet*, 1, 674, 1935; Eng, H.: *Biochem. Ztschr.*, 274, 208, 1934. (3.) Ferrigno, P.: *Clin. Ostetrica*, 37, 129, 1935. (4.) Kemp, T., and Pedersen-Bjergaard, K.: *Endokrinologie*, 13, 156, 1933. (5.) Robson, J. M., MacGregor, T. N., Illingworth, R. E., and Steere, N.: *Brit. Med. J.*, 1, 888, 1934. (6.) Zondek, B.: *Lancet*, 2, 356, 1934. (7.) Mazer, C., and Israel, S. L.: *J. Am. Med. Assn.*, 108, 163, 1937. (8.) Smith, G. van S., and Smith, O. W.: *Am. J. Physiol.*, 112, 340, 1935. (9.) McClendon, J. F., Burr, G., and Conklin, C.: *Proc. Soc. Exp. Biol. and Med.*, 26, 265, 1928. (10.) Frank, R. T., Goldberger, M. A., and Spielman, F.: *Ibid.*, 29, 1229, 1932. (11.) Silberstein, F., Molnar, K., and Engel, P.: *Klin. Wehnschr.*, 12, 1694, 1933. (12.) Fee, A. R., Marrian, G. F., and Parkes, A. S.: *J. Physiol.*, 67, 377, 1929. (13.) Starling, E. H., and Verney, E. B.: *Proc. Roy. Soc. B*, 97, 321, 1925. (14.) Zondek, B.: *Skand. Arch. f. Physiol.*, 70, 133, 1934. (15.) Rondoni, P., Carminati, V., and Corbellini, A.: *Ztschr. f. Physiol. Chem.*, 241, 71, 1936. (16.) Plehn, A.: *Archiv f. Schiffs- und Tropen-Hygiene*, 11, 763, 1907. (17.) Knowlton, F. P., and Starling, E. H.: *J. Physiol.*, 44, 206, 1912. (18.) Priestley, J. T., Markowitz, J., and Mann, F. C.: *Am. J. Physiol.*, 96, 696, 1931. (19.) Bellet, S., Ravdin, I. S., McMillan, T. M., and Morrison, J. L.: *Am. J. Med. Sci.*, 185, 636, 1933. (20.) Kiese, M., Gummel, H., and Garan, R. S.: *Arch. f. Exp. Path. u. Pharm.*, 184, 197, 1937. (21.) Frank, R. T., and Goldberger, M. A.: *J. Am. Med. Assn.*, 87, 1719, 1926. (22.) Allen, E., and Doisy, E. A.: *Am. J. Physiol.*, 69, 577, 1924. (23.) Cohen, S. L., and Marrian, G. F.: *Biochem. J.*, 30, 57, 1936.

HEREDITARY HYPOPLASIA, OF THE MESENCHYME.

(BLUE SCLEROTICS AND BRITTLE BONES.)

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Louisiana, and from the Charity Hospital of Louisiana.)

In a 14-year-old white boy under treatment for acute hemorrhagic nephritis, blue scleræ were noted on physical examination. Further study showed that he had a fracture of the humerus 5 years previously. Roentgen ray examination revealed a moderate degree of arthrokatadysis (Otto's pelvis). A search of the family history disclosed the presence of blue scleræ in the brother and mother. A more careful analysis of the family tree led to the discovery of a group of individuals with hereditary hypoplasia of the mesenchyme, which group is larger than any we have been able to find in the literature. Because of the rarity of the condition and size of the family tree, we believe a brief report of our findings is warranted.

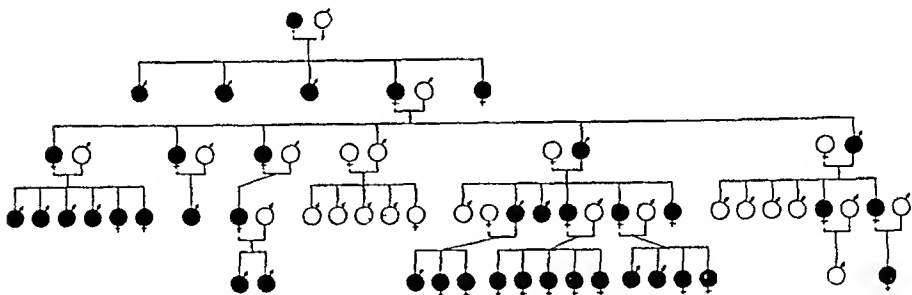


CHART I.—Family tree showing affected (black) and normal (white) individuals. Twenty-three normal members of the fifth generation, children of normal individuals of the fourth generation, are not shown.

Of 76 known individuals in the family, 53 are shown in the accompanying figure. The 23 individuals not illustrated were normal offspring of normal members shown in the fourth generation. These 23 individuals were omitted from the illustrated family tree because of insufficient sex data. Of the 76 people studied, 41 (53.9%) were found to be affected. Five affected members of the fourth generation, shown in the figure on the left, had many affected children.

Our information regarding the children is meager because of their inaccessibility, so that they could not be included in this presentation.

Every affected individual had an affected parent. The disease was transmitted 10 times by females and 3 times by males. Of the 41 affected individuals, 17 were males and 24 were females. This is in keeping with previous reports.^{1,2} All of those affected had blue scleræ; 17 of them are known to have had one or more fractures. Our patient and his mother, grandmother and great-grandmother had varying degrees of deafness. The relative frequency of deafness for the entire group is unknown. Three of the affected individuals were small in stature with large skulls and prominent bossæ. This, however, was not true throughout the family tree. There was no evidence of hypermobility of joints as far as could be determined.

Comment. Idiopathic bone fragility is classified as follows:¹

I. *Hereditary type*: 1. Hereditary hypoplasia of the mesenchyme (Brittle bones and blue scleræ).

II. *Non-hereditary congenital type*: 1. Osteogenesis imperfecta congenita. 2. Osteogenesis imperfecta tarda (osteopsathyrosis): a, With white scleræ; b, with blue scleræ.

III. *Non-hereditary acquired type*: 1. Osteosclerosis fragilis generalisata (Marble bones, or Albers-Schönberg's disease).

IV. *Senile type*: 1. Osteoporosis.

Our group is an example of the hereditary type. The heredity of the disease behaves according to the Mendelian law for a single dominant factor which is not sex-linked. The clinical picture is characterized chiefly by: 1, blue scleræ; 2, fragility of bones; 3, deafness, and 4, hypermobility and relaxation of joints. All affected persons have blue scleræ, but the other characteristics are variable. This proved to be true in our group. The blueness of the sclera is ascribed to hypoplasia of the sclerotic mesenchyme with a resulting thinness of the sclerotic coat which permits the choroid pigmentation to shine through. Similarly the hypoplasia of the mesenchyme explains the ease of fracture of the bones and the relaxation of the ligaments. While the affected individuals are usually described as small in stature, this was not true in many of the members of our group.

Summary. Of 76 known individuals in five generations of the family studied, 41 (53.9%) were affected with hereditary hypoplasia of the mesenchyme. This is a larger group than any we have been able to find in the literature.

REFERENCES.

- (1.) Hills, R. G., and McLanahan, S.: Arch. Int. Med., 59, 41, 1937. (2.) Key, J. A.: Arch. Surg., 13, 523, 1926.

THE TISSUE PRESSURE IN SUBCUTANEOUS EDEMA.

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IN the mechanisms concerned in the control of fluid exchange across the small blood-vessel walls, the interplay of the osmotic pressure and hydrostatic pressure of the blood has been accepted as the major controlling force. The influence of comparable forces in the tissue outside of the blood-vessels has been largely neglected. The colloid osmotic pressure of the interstitial tissue fluids has been studied satisfactorily only in patients with edema where fluid sufficient for analysis has been collected. The amounts of interstitial fluid in the normal individual are so small that accurate analyses have been impossible. Tissue pressure, which is related to hydrostatic pressure within the blood-vessels, has only recently been directly determined in this country.^{1a,b} It is with the influence of the latter factor, tissue pressure, that the present report is concerned.

Methods and Materials.—The method used in these determinations is that previously described.^{1b} It consists essentially of a U-tube water manometer connected by rubber tubing to a rubber pressure bulb controlled by a screw clamp and also connected to a glass adapter to which is fastened a 26-gauge needle. The opening in the bevelled end of the needle was occluded with solder and 4 openings symmetrically drilled into the lumen through the wall of its distal third. In use, sterile normal saline was drawn into the needle and about half way up the adapter and the pressure in the system was then brought to atmospheric. The needle was then inserted into the subcutaneous tissues of the part to be studied and the pressure within the system was slowly raised by the screw clamp until the meniscus in the adapter just began to move. This pressure was taken as the subcutaneous tissue pressure. All determinations were made under aseptic technique. Three readings were taken which agreed within ± 1 mm. of water for each determination. The part rested passively without movement or constriction throughout the determination.

Determinations were made on 23 subjects with various types of edema. Only subjects with increasing edema were chosen. With 2 exceptions all determinations were made in the pretibial area in patients confined to bed. In the patients with histamine edema

(0.5 cc. of 1 to 1000 histamine phosphate subcutaneously) and with scleroderma, the determinations were made in the arm. The causes of the edema were as follows: congestive heart failure, 10; acute hemorrhagic nephritis, 3; low serum proteins, 2; beriberi, 2; operative trauma, 2; pernicious anemia, 1; toxemia of pregnancy, 1; erysipelas, 1; histamine, 1. The edema of operative trauma developed in 1 patient with marked scleroderma following a stellate ganglionectomy, and in another patient following the removal of a tumor about the ankle.

TABLE 1.—SUBCUTANEOUS TISSUE PRESSURE DETERMINATIONS IN VARIOUS TYPES OF EDEMA.

Subject No.	Cause of edema.	Day of observation.																	
		1	2	3	4	5	7	8	9	10	11	12	13	14	16	20	21		
1	Cong heart fail.	181	188	148	Died														
2	Cong. heart fail.	126	122	42	32	60	58												
3	Cong. heart fail.	60	Died																
4	Cong. heart fail.	208	242	..	194	180	Died										
5	Cong. heart fail.	116	52	..	52	98	..	69											
6	Cong. heart fail.	156	140	142	..	106	100	Died	58	..	70	..	64	49			
7	Cong. heart fail.	110	..	40	38	40													
8	Cong. heart fail.	218	202	..	218	86		
9	Cong. heart fail.	70	..	50	..	50	52	44	36			
10	Cong. heart fail.	47	58			
11	Beriberi	124	68	50	38		
12	Beriberi	86	42			
13	Nephritic	102	51			
14	Nephritic	106			
15	Nephritic	94			
16	Nephrotic	78	150	..	Died			
17	Nephrotic	62	..	61			
18	Scleroderma	280	*	338			
19	Per. anemia	114	158	122	150	216		
20	Tox. preg.	88	161	102	36			
21	Post. op.	41	26			
22	Erysipelas	188			
23	Histamine	246			

* Cervical sympathectomy performed.

Italicized numbers indicate that the patient was edema-free.

Results. (Table 1.) The extremes of the values in the patients with cardiac edema and the course of the tissue pressure in 5 of them were previously reported.¹⁶ In all the subjects studied with increasing edema, regardless of the cause, the tissue pressure was elevated. The values varied from 41 to 338 mm. of water, the lowest value being obtained in the patient with postoperative edema following the removal of a tumor of the ankle, and the highest value in the patient with scleroderma and postoperative edema.

The mean values of tissue pressure for the various groups would be misleading in that there is a great variability in the phase and extent of the edema. As shown previously, in cardiac edema¹⁶ the tissue pressure correlated closely with the clinical state of the edema. In increasing edema, the tissue pressure increased; in subsiding edema, the tissue pressure fell. This was also found to be true in patients with other types of edema.

Discussion. The normal values for the subcutaneous tissue pressure in the volar surface of the forearm and pretibial area at heart

level were found to vary from 11 to 54 mm. of water.^{1b} With one exception, the values in all types of edema studied exceeded these limits. In 1 patient with postoperative edema of the foot, the value with edema was 41 mm. of water. One week later, when he was clinically edema-free, the value fell to 26 mm. of water. This illustrates the fact that patients may develop edema with a tissue pressure elevated above their original level, yet not exceeding that found in certain normal individuals. This is particularly true in receding edema.

If there is an increase in interstitial fluid, the tissue pressure must increase unless the tissues stretch equally for an equal increment in volume and still offer the same rebounding force, or unless the tissues stretch equally with each increment without a rebounding force. Since, within the limits of clinical edema, tissues do not function in this manner, the addition of interstitial fluid will elevate the tissue pressure to an extent dependent on the three following factors: 1, increase in filtration, 2, distensibility of the surrounding tissues, and 3, the rate at which interstitial fluid is removed, for example, through the lymphatics. As the fluid accumulates, tissues are displaced and the fibrous network is stretched, the tissue tension increases and this, in turn, alters the filtration and removal rates. The interplay of these three factors influences the level to which tissue pressure may rise.

The increase in filtration rate is dependent upon a disturbance in the equilibrium between the filtration, hydrostatic pressure of the small blood-vessels and the osmotic pressure of the tissue fluids, and antifiltration, osmotic pressure of the blood colloids and the tissue pressure. Changes in permeability of the capillary wall also change the filtration rate through their influence upon these factors. In cardiac edema, the essential disturbance has been ascribed to increased hydrostatic pressure; in nephrotic edema, reduction in plasma colloid osmotic pressure disturbs this equilibrium; in nephritic edema, the generally accepted explanation is an increased capillary permeability resulting in an increased osmotic pressure of the tissue fluids. As far as we know, there is no clinical state in which edema develops primarily upon the basis of reduced tissue pressure. However, in increasing edema, tissue pressure rises and becomes increasingly significant in the reestablishment of a filtration-antifiltration equilibrium. The height to which tissue pressure may rise is dependent, as previously stated, upon the distensibility of the tissues and the rate at which interstitial fluid is removed, as well as the magnitude of pressure change disturbing the filtration-antifiltration equilibrium.

Since the tissues are imperfectly elastic, as fluid accumulates and they are stretched, they become less distensible. Tissue pressure then rises and tends to equalize the filtration pressure, acting as a limiting factor to the extent of the edema. The loss of dis-

tensibility in the skin is one of these important limiting factors. The shiny smooth stretched skin of the legs of patients with marked cardiac edema is clinical evidence of this point. With stretching and displacement of the tissues, particularly for long periods of time, these structures may lose part of their elasticity so that in receding edema abnormal amounts of interstitial fluid may be present under normal tissue pressure. This may account for our findings of normal tissue pressure in the presence of clinical edema in some of the patients in Table 1.

The third factor regulating the height to which tissue pressure may rise, the rate at which interstitial fluid is removed, as through lymphatics, has not been measured quantitatively in relationship to the other two factors. Therefore, its place and importance in influencing the tissue pressure is not established. As is well known, edema upon this basis alone does occur.

It appears that in areas with very high tissue pressures, such as in scleroderma with a tissue pressure of 338 mm. of water, or in the histamine area with a value of 246 mm. of water, with normal intravascular pressures the capillaries and veins would collapse. However, in histamine edema, the intravascular pressures are elevated locally,^{2,3} and the integrity of the circulation in that area is maintained. In scleroderma, in the face of tissue pressure exceeding the normal intravascular pressure of the small vessels, the pressure in these vessels must necessarily increase to maintain the circulation. In the patient with scleroderma, before edema developed the tissue pressure determination was 280 mm. of water. One might state that the tissue pressure in this area was in the normal range but that when the fluid was introduced in the determination there was an inability of the more fibrous and less elastic structures to accommodate the increased volume, with a sudden steep rise in pressure. In such a situation, the determined pressure would not represent the actual pressure of the tissues, that is, for example, the pressure on the contained blood-vessels. Determinations of the pulse volume at heart level in the finger tip of this patient showed pulsations lower than the average normal range, both before and after sympathectomy. With development of edema and a rise of tissue pressure to 338 mm. of water, the pulsations remained essentially unchanged. Were the tissue pressure originally within normal range and elevated through introduction of edema into an unyielding tissue, the pulsations would have decreased markedly. This is evidence that the tissue pressure in this patient was actually elevated, aside from the decreased distensibility of the tissues when fluid was further introduced into them.

In tissues with very low distensibility, such as bone, calcified areas, and the epidermis, introduction of small amounts of fluid may cause the tissues rapidly to reach the state of maximum distensibility and give erroneously high results. In the tissue we have

studied, the subcutaneous area, even in scleroderma, such factors are apparently not significant with the small needle employed and negligible amounts of fluid injected.

Summary and Conclusions. In 23 patients with various types of edema, we found an elevation of the subcutaneous tissue pressure in the edematous areas. The tissue pressure was found to vary with the state of the edema.

Tissue pressure appears to be a factor in the regulation of the interchange of fluid between the blood-vessels and tissue spaces. It becomes increasingly significant with the accumulation of the interstitial fluid.

The height to which tissue pressure may rise depends upon the interplay of at least three factors: 1, increase in filtration across the capillary membrane; 2, the distensibility of the surrounding tissues; 3, the rate at which interstitial fluid is removed, for example, through the lymphatics.

REFERENCES.

- (1.) Burch, G. E., and Sodeman, W. A.: (a) *Proc. Soc. Exp. Biol. and Med.*, 36, 256, 1937. (b) *J. Clin. Invest.*, 16, 845, 1937. (2.) Ellis, B., and Weiss, S.: *Ibid.*, 8, 47, 1929-1930. (3.) Landis, E. M.: *Heart*, 15, 209, 1929-1931.

BOOK REVIEWS AND NOTICES.

THE ART OF TREATMENT. By WILLIAM R. HOUSTON, A.M., M.D., F.A.C.P.
Formerly Professor of Clinical Medicine, University of Georgia; Formerly
Visiting Professor of Medicine, Yale-in-China. Pp. 744. New York:
The Macmillan Company, 1936. Price, \$5.00.

THIS is the most interesting medical text that has come to the Reviewer's attention in several years. It is the ambition—and only too often the despair—of every teacher of medicine to impart to his students not merely knowledge, but wisdom in its application, the wisdom gained by years of experience and which is the essence of the art of medical practice. Not a few teachers are able to achieve this aim in clinical lecture or ward walk, but only rarely can this be said of the printed page. It certainly can be said of this book, and in superlative terms.

The manner of presentation is unusual, interesting and effective. The first section deals with general principles under such headings as Scope of Therapeutics, Therapeutic Thinking, Diagnosis, Honesty, Economics, The Doctor as a Therapeutic Agent; it proves the author to be not only a master clinician but also a philosopher, and a facile wielder of the pen. Then follow sections on "Patients who are to be treated chiefly by Nursing Care" (e. g., typhoid fever, inoperable carcinoma); "Specifics" (animal parasite diseases, specific sera, endocrinopathies, etc.); "Conditions in which the Chief Therapeutic Method is Psychotherapy or Guidance" (the organ neuroses, hysteria, neurasthenia, etc.)—this section is superbly handled, with numerous illustrative case reports and a splendid discussion of the practicability of psychoanalysis; "Diseases which impose a Limitation upon Life as the Condition of Treatment" (obesity, heart disease, tuberculosis, old age, etc.); "Disorders in which Physiological Considerations Guide Treatment" (peptic ulcer, the diarrheas, gout, kidney diseases, etc.); and "Conditions in which Treatment is Tentative and Experimental" (the case where the diagnosis is uncertain; arthritis; allergic diseases; the neuralgias, etc.). Obviously the author "had much doubt as to classification," and his invitation that the reader challenge the classifications will call forth an abundant response [so why Hodgkin's disease and the leukemias among those for which there are specifics?], but in the main the reader will agree with the author.

There are some minor criticisms. Obviously no internist can be equally skilled in the treatment of all the diseases in this field and that is bound to produce a certain unevenness in emphasis, or at least in space allotment. So the author, a masterful practical psychiatrist, devotes 240 pages, a third of the book, to the conditions treated chiefly by psychotherapy and guidance—it is the best-done section of the book—but physiotherapy gets only half a page. The author seems unduly conservative about the serum treatment of pneumonia and too skeptical of the value of plasmochin and atabrine in malaria. There is no mention of adrenal cortical hormone on the treatment of Addison's disease, or of vaccine for the prophylaxis of whooping cough. He knows little about allergy, and much of that little "ain't so." Venoclysis certainly does not require the routine exposure of the vein by an incision. Not all would agree that diphtheria and tetanus antitoxins are the only sera of enough therapeutic value to warrant being given intravenously (what of antipneumococcic and antimeningococcic sera?). The repeated use of the word "pathology" as a synonym for "lesion" offends the purist.

The type setter has contributed an error in listing "Foot and Mouth Diseases" among the rare conditions to be treated chiefly by nursing care.

But these are trifling criticisms and should in no way detract from the value of the book as a whole. It was not written to be a mere repository of information, in which to learn at a glance "what is good for this or that," but to give a viewpoint of therapeutics, a philosophic presentation of the art of treatment, and this it does admirably. It is a masterpiece. All physicians, but especially all young physicians, and senior students should read and re-read this volume.

R. K.

THE BRITISH ENCYCLOPÆDIA OF MEDICAL PRACTICE. Vol. 4. Diarrhœa to Endoscopy of the Rectum. Under the General Editorship of SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge, etc., with five assistants in a consultative capacity. Pp. 650; 129 illustrations. London: Butterworth & Co. (Publishers), Ltd., 1937. Price, \$12.00.

THE fourth volume of this noteworthy Encyclopedia embraces 42 articles, on subjects arranged alphabetically from "Diarrhœa" to "Endoscopy of the Rectum." The contributors are mostly from London and almost exclusively English. The opinions expressed in Reviews of previous volumes (*Am. J. Med. Sci.*, 193, 711, 1937; 194, 123, 1937) can be reiterated for the present volume.

E. K.

DEXTROSE THERAPY IN EVERYDAY PRACTICE. A Survey of the Literature, 1900-1936, on the Experimental and Clinical Studies Applicable to Medicine and Surgery. By E. MARTIN, Sc.D., New York. With forewords by W. N. HAWORTH, F.R.S., Director of the Department of Chemistry, University of Birmingham (Eng.) and BERNARD FANTUS, M.D., Professor of Therapeutics, University of Illinois, College of Medicine. Pp. 451; 44 illustrations including 15 full-page plates. New York: Paul B. Hoeber, Inc., 1937. Price, \$3.00.

THIS volume on a subject of interest to both practitioners and research workers forms a welcome addition to medical literature. The author has endeavored, and has succeeded exceedingly well, to correlate the more important experimental and clinical studies on the subject of dextrose therapy. There is an extensive review of the literature. The volume deals with various aspects of normal and abnormal physiology with which glucose therapy is concerned. It is often difficult to present material which is still controversial but the author has done this in an admirable manner by presenting by preference the present trend of thought rather than attempting to introduce his personal conclusions.

Besides the preface and two forewords there are fourteen chapters and an Index of Personal Names and Index of Subjects. Appended to each chapter is an excellent bibliography.

Without doubt the work will be of greater usefulness to the medical practitioner than to the research worker. There are certain aspects of the chemistry of glucose absorption which have been hastily covered and other aspects which may be proven to be incorrect, but these do not detract from the usefulness of the volume to practitioners. The chapter on "Physiological Action" on the whole forms an excellent background for those not familiar with much of the recent work which has been done. While no attempt has been made to discuss dextrose therapy in every condition where it may prove useful the many pathological conditions reviewed in the volume and the presentation of the subject matter is to be commended.

The Reviewer was especially interested in the chapter on Dextrose in Surgery which should prove very valuable. The accuracy with which the literature has been searched can be seen when he states "the value of dextrose in preventing and alleviating crises (thyroid), first realized clinically by Frazier in 1931," for a number of papers published since that time fail to mention the original paper.

I. R.

FAILURE OF THE HEART AND CIRCULATION. By TERENCE EAST, M.A., D.M., F.R.C.P., Physician, King's College Hospital and Woolwich Memorial Hospital. Pp. 130. London: John Bale, Sons & Curnow, Ltd., 1937. Price, 2/6.

THIS little book contains a surprisingly comprehensive account of the various ways in which cardiovascular function may be affected by disease, together with the methods of treatment. Indeed it is almost as complete a treatise as many of the larger works on the same subject. Written from a definitely physiological point of view, the presentation is nevertheless essentially clinical and well adapted to the practical requirements of the physician in general practice. The convenience of size, however, is not an unmitigated advantage; the style is almost telegraphic which makes rather tiresome reading, while the sections on treatment are in many places so condensed that they seem unsatisfactory as a source of reliable therapeutic advice. In general, the explanations of circulatory and cardiac disorders are those currently held in this country, although recent teaching has tended to disparage the use of some of the drugs which are mentioned, particularly the proprietary extracts of digitalis. The book undoubtedly deserves recommendation to practitioners and students whose limited time precludes reference to more detailed literature.

L. L.

PATHOLOGY. (Vol. XIX of *Clio Medica* Series.) By E. B. KRUMBHAAR, M.D., Professor of Pathology, University of Pennsylvania School of Medicine. Pp. 206; 18 illustrations. New York: Paul B. Hoeber, Inc., 1937. Price, \$2.00.

To survey so great a subject through all the ages in so brief a book as this must be very difficult, but the author has succeeded admirably. The slow progress through the centuries is halted, sometimes for long periods, by the positive statements of some influential figure whose certainty has blocked advance. Such was the dogmatism of Galen, which recalls the words of Goethe—"one is sure only when one knows very little about a subject." Great names stand out, sometimes of those who have made real, enduring contributions, such as Morgagni, Hunter, Cohnheim and Pasteur, sometimes of those whose engaging personalities have brought them fame and followers.

But since Pathology necessarily depends upon the advance of knowledge in all such fundamental subjects, a physics, chemistry and biology and more nearly upon anatomy and physiology, its progress must await theirs. Pathological anatomy remains necessary as the end result, but to appreciate its nature we must learn the course of events that led to its divergence from normal anatomy, and then reflect upon the disturbances that it has caused in the even trend of life. And hence it is, that while in earlier times interest was concentrated upon these distorted organs which were lightly referred to disproportions of the four humors or to dyscrasias, perhaps from the *pneuma*, every effort is now directed toward the discovery of the cause. More might have been said of the stirring advances of recent years, almost

always based on the etiology of disease, although the recognition of the numerous mechanisms for reaction, varying in character and intensity according to the nature of the injurious agent, and the relatively uniform mechanism of repair, has rounded out the picture.

The chronological tabulation of noteworthy contributions is of great interest, and with its aid the gradual progress may be surveyed. With this some reference to the great works on the history of medicine, such as those of Haeser, Neuburger and Pagel, etc., might have been given. But from none of these colossal volumes can one draw, as in this little book, so clear a picture of the long trail which has led us at least to the realization of an equally long road to go in the future. W. M.

DR. BODO OTTO and the Medical Background of the American Revolution.

By JAMES E. GIBSON. Pp. 345; illustrated. Springfield, Ill.: Charles C Thomas, 1937. Price, \$4.00.

In 1755, Bodo Otto, then 44 years of age and a physician of repute in Germany, emigrated to America with his family. He practised medicine in and about Philadelphia until the outbreak of the Revolution when he became a military surgeon in the American Army. He served with distinction throughout the war and on its close resumed his practice in Philadelphia and Baltimore. He died in Reading in 1787. The heroic service which he rendered to his fosterland has scarcely received the recognition which it so well deserved.

The biography of Doctor Otto is the theme around which the author's narrative is expanded to include a brief but picturesque history of Hanover, pre- and post-revolutionary medicine in America, and the story of the medical department of the Continental Army with all its incredible difficulties, its bitter intrigues and its hard-won accomplishments. The reader appreciates, as perhaps never before, how large a part the ravages of epidemic diseases have played in the success and failure of the military campaigns of the past. In the light of contemporary discussion of the morality of spreading disease as a weapon of modern warfare, it is interesting to note that the British were accused of sending persons infected with smallpox into the American camp around Boston in an effort to spread infection among the troops.

This book represents an enormous amount of research into the documentary records of the period which are liberally quoted throughout. Such quotations greatly enhance its value from the academic aspect, at the same time removing it from the category of comparable works which are primarily designed to be easily read. L. L.

THE COST OF ADEQUATE MEDICAL CARE. By SAMUEL BRADBURY, M.D.

Pp. 86; 13 tables. Chicago: The University of Chicago Press, 1937. Price, \$1.00.

THE extensive studies conducted by the Committee on the Costs of Medical Care were concerned largely with an analysis of the expenditures for medical care in this country, with the hope of finding ways and means by which these expenditures could be reduced and better distributed. The ultimate objective of these important studies was to see what could be done to make adequate medical care available to the entire population. Calculations were made which indicated that "the cost of complete Medical Care" should be \$36.00 a year per person.

Bradbury has restudied this question, and has used the study of Lee and Jones on *The Fundamentals of Good Medical Care* as the basis for his study, as giving the best estimate of the amount of medical care needed by the people of this country. He has translated the amount of adequate

medical service as estimated by Lee and Jones into its cost, by applying the schedule of minimum fees for medical service of the Chicago Medical Society.

The question of costs is ably analyzed from various aspects and much clear light is thrown on the annual expense of maintaining an adequate health service in this country. He comes to the conclusion that, in order to carry out a service which is thought by representative members of the medical profession to meet actually the medical needs of this country, an annual expenditure of \$9,500,000 is required, instead of the \$3,700,000 now expended by the American people each year for this purpose. Instead of \$36.00 a year per person, which has been widely quoted as the sum needed to provide adequate medical service, actually \$75.75 per person a year is required, for prevention, diagnosis and treatment of illness.

It is necessary to examine carefully Bradbury's calculations and formulations to understand this intricate problem to which he has given careful attention, and anyone interested in the economic problems of medical service must give this little volume careful reading. It is fortunate that Bradbury's study has been made before too much has been planned or erected on the insecure foundation of the previous estimates, the omissions of which are pointed out.

G. R.

PHYSICAL DIAGNOSIS. By DON C. SUTTON, M.S., M.D., Associate Professor of Medicine, Northwestern University School of Medicine, Chicago. Pp. 495; 298 text illustrations, and 8 colored plates. St. Louis: The C. V. Mosby Company, 1937. Price, \$5.00.

"ANOTHER textbook of Physical Diagnosis," this one is distinguished by an excellent historical introduction by Dr. Irving S. Cutter, a profusion of well selected illustrations, and an adequate text.

In the opinion of the Reviewer, history taking cannot and should not be taught in the course in physical diagnosis as long as most medical schools teach this subject at the beginning of the second year. It is unreasonable to expect students to take anything like an adequate or even intelligent history when they have had absolutely no instruction in clinical subjects. The teaching of history taking should be part of the curriculum of the third year, marking as it does the student's first contact with the problems of clinical medicine in the Out-Patient Departments or the Wards.

It is noted with satisfaction that Dr. Sutton has successfully avoided the usual temptation to include in a textbook of physical diagnosis an abridged and almost always a useless textbook of medicine.

The ideal textbook of physical diagnosis will be written when the author confines himself strictly to the subject and when the physics of sound are adequately described and correlated with physical signs. "Norris and Landis" alone have achieved this in their physical diagnosis of the heart and lungs but they failed to realize that the human body is not bounded on the North by the pulmonary apices and on the South by the costal margins.

S. L.

THE ALIMENTARY FACTOR IN DISEASE. By MAX H. KUCZYNSKI, M.D., D.Sc., Pathologist to the Ministry of Public Health of Peru; Professor of Physiopathology at the University of San Marcos, Lima, Peru, etc. Pp. 130. Second Edition of "Studies on Nutrition." The Hague: G. Naeff, 1937. Price, 3 Guilders.

In 12 chapters the author presents his belief that alterations in nutrition are responsible for the manifestations of yellow fever, poliomyelitis; diphtheria, trypanosomiasis, baldness, gastric ulcer and appendicitis; that amyloid disease may be produced or relieved at will by alterations in the

diet and that most cellular functions "have their origin in variations of cellular nutrition." Unfortunately the specific alterations in nutrition which the author has in mind are rarely stated. Vitamin B₁ deficiency, however, is one that the author considers at some length, his contention being that, because the manifestations of this deficiency frequently resemble those of yellow fever, poliomyelitis and the other conditions mentioned above, these diseases must be due primarily to such deficiency. The author has apparently long been an observer in many fields and has exerted enthusiastic curiosity in searching for explanations of his observations. His conclusions, however, are reached through deduction rather than demonstration and therefore are not impressive; yet his monograph may be of value in stimulating careful investigation of the relationships which he suggests. Frequent typographical errors and lack of organization in presentation of the material make reading difficult. K. E.

OBSTETRIC AND GYNECOLOGIC NURSING. By FREDERICK H. FALLS, M.S., M.D., F.A.C.S., Professor of Obstetrics and Gynecology, University of Illinois College of Medicine; Attending Gynecologist of the Illinois Research and Educational and Cook County Hospitals, etc., and JANE R. McLAUGHLIN, B.A., R.N., Supervisor of the Department of Obstetrics and Gynecology, Research and Educational Hospitals, and Instructor in Department of Obstetrics, University of Illinois College of Medicine, etc. Pp. 492; 83 illustrations by Charlotte S. Holt. St. Louis: The C. V. Mosby Company, 1937. Price, \$3.00.

THE field of obstetrics and gynecology is difficult to cover in a limited space. For students this book necessarily leaves considerable material to be clarified during class instruction.

Routine abdominal palpation and resuscitation of the newborn are evidently regarded as procedures better taught by demonstration than by text book description. I believe some space could advantageously have been devoted to a discussion of present trends in obstetric analgesia.

The chapter on home delivery gives excellent directions for preparation and care during delivery. I especially enjoyed the illustrations. The well drawn sketches present important details more clearly than the usual photograph. W. E.

GASTROSCOPY. The Endoscopic Study of Gastric Pathology. By DR. RUDOLF SCHINDLER, Associate Clinical Professor of Medicine, University of Chicago; Attending Gastroscopist, Michael Reese Hospital; Consulting Gastroscopist, Cook County Hospital, Chicago. With a Preface by DR. WALTER LINCOLN PALMER, Associate Professor of Medicine, University of Chicago. Pp. 343; 89 text figures and 96 color reproductions of gastroscopic observations, with legends. Chicago: The University of Chicago Press, 1937. Price, \$7.50.

As the first textbook in English on modern gastroscopy and as the product of one of the originators of the flexible gastroscope, who had previously had on the European continent an extensive experience with other types of gastroscopic apparatus, this work must be regarded as constituting for the English speaking profession a standard reference work. It is simply and clearly written, and includes not only what appears to be a fair statement of the history of the development of clinical gastroscopy and a detailed description of the technique for the use of the flexible instrument but also a consideration, from the endoscopist's viewpoint, of all the important

diseases of the stomach. Although further experience by the author and other gastroscopists will undoubtedly lead to many alterations of opinion as to the significance of certain observations and perhaps to a more restricted list of indications for the use of the gastroscope than Schindler in his enthusiasm now advocates, no one can question that he has developed and made available to others a method of investigation for gastric disease that rivals and at the same time supplements the Roentgen ray. The book should be read by every internist and general surgeon and it will be found indispensable to all those doing endoscopy of the stomach.

T. M.

DISEASES OF THE NERVOUS SYSTEM IN INFANCY, CHILDHOOD AND ADOLESCENCE. By FRANK R. FORD, M.D., Associate Professor of Neurology, The Johns Hopkins University. Pp. 953, 107 illustrations, 14 charts and 14 tables. Springfield, Ill.: Charles C Thomas, 1937. Price, \$8.50.

REALIZING that neurological study of early life has not had sufficient consideration, the writer draws from his own large experience and in addition, assembles and analyzes a vast amount of relevant material. The usual anatomical classification is replaced by one primarily etiological. Appended to each chapter is a carefully selected bibliography with preference given to those references in English, and it is here, almost exclusively, that controversial subjects appear. The contents is discussed in thirteen chapters: Examination. Clinical Aspects of Anatomy and Physiology. Prenatal Diseases. Heredofamilial and Degenerative Diseases. Infections and Parasitic Invasions. Toxic and Metabolic Disorders. Vascular Lesions and Circulatory Disorders. Neoplasms. Injury by Physical Agents. Epilepsies and Paroxysmal Disorders. Diseases of the Autonomic System. Diseases of the Muscles. Syndromes and Symptom Groups. Most space is allotted to Infections and Parasitic Invasions, with the classification primarily upon etiology and secondarily upon pathological anatomy. Only those disorders are included in which it is thought the etiological agent has invaded the nervous system. Epidemic encephalitis is considered as Type A and Type B, both believed due to a filterable virus; the latter, as reported in the Japanese epidemic and that of St. Louis, 1933, clinically, appears to differ from the former. Considered in conjunction with these, is the Australian X disease, with symptoms more closely allied with Type B. However, all may be variants of the same disease. The chapter on Neoplasms and Related Conditions, is replete with case histories—thirty-one in fact. Sixty-five per cent of brain tumors, showing symptoms before fifteen years, are cerebellar in origin. During adult life, the percentage of cerebellar tumors falls, while the number of cerebral growths slowly increases. Seventy-five per cent of all intracranial tumors of childhood are gliomas; of those remaining, 13% are hypophyseal duct cysts; 5% tuberculomas; 4% pinealomas; most of those remaining are papillomas of the choroidal plexus, hemangioblastomas, meningiomas and metastatic growths. Considerable space is given to poisoning by lead, arsenic, bismuth and thallium, and rabies occupies more than four pages; but some of the functional disorders, notably hysteria—even seen in the fifth year—receive no definite consideration. Disorders of Behavior are given a heading, though discussed but little there or elsewhere. Much of the last chapter is but a repetition. However, these for the most part are minor matters. For the first time in English this excellent volume brings together the nervous disorders of infancy, childhood and adolescence, and it doubtless will become the popular book for diseases of these periods.

N. Y.

NEW BOOKS.

General Hygiene and Preventive Medicine. A Text-book for College Students, Medical Students, Nurses, Public Health Workers and Social Workers. By JOHN WEINZIRL, M.S., PH.D., DR.P.H., late Professor of Bacteriology and Director of the Alice McDermott Foundation of the University of Washington; Technical Adviser on Public Health to the Washington State Planning Council, etc. Edited by ADOLPH WEINZIRL, B.S., M.D., C.P.H., Health Officer, Portland, Ore.; Clinical Professor of Public Health, University of Oregon Medical School, etc. Pp. 424. Philadelphia: Lea & Febiger, 1937. Price, \$4.00.

The Therapeutic Problem in Bowel Obstructions. A Physiological and Clinical Consideration. By OWEN H. WANGENSTEEN, B.A., M.D., PH.D., Professor of Surgery of the University of Minnesota and Surgeon-in-Chief of the University of Minnesota Hospital. Pp. 360; 90 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price, \$6.00.

Neuere Ergebnisse auf dem Gebiete der Krebskrankheiten. (Fortbildungskurs der Berliner Akademie für ärztliche Fortbildung [vom. 19 bis 26. Oktober. 1936].) Herausgegeben von PROF. DR. C. ADAM und PROF. DR. AULER. Forty-four contributors. Mit einem Vorwort von Geheimrat PROF. DR. BORST, München. Pp. 366; illustrated. Leipzig: S. Hirzel, 1937, Price, Paper, Rm. 12; Bound, Rm. 13.50.

Curieterapia in Dermatologia. By PROF. VINCENZO PALUMBO, Direttore Istituto Radioterapico Italiano. Pp. 87; 76 illustrations. Belluno: A. Salvador, 1937. Price, Paper, L. 30; Bound, L. 36.

Acta Neerlandica Morphologiae. Normalis et Pathologicae, Vol. 1, No. 1 (1937). Edita A. H. T. DEELMAN, Prof. Anat. Pathol. Amsterdam; J. DE HAAN, Prof. Histol. Groningen; G. KREDIET, Prof. Anat. et Histol. veter. Utrecht, et M. W. WOERDEMAN, Prof. Anat. et Embryol. Amsterdam. Pp. 96; illustrated. Utrecht: N. V. A. Oosthoek's Uitgeversmaatschappij, 1937. Price: Netherl. guilders 20. per volume.

The One Hundredth Anniversary of the Army Medical Library, Washington, D. C., 1936. Pp. 130; illustrated.

A pleasant souvenir of an important occasion.

The Postmortem Examination. By SIDNEY FARBER, M.D., Associate in Pathology, Harvard Medical School; Pathologist to The Infant's Hospital and The Children's Hospital, Boston. Pp. 201; 32 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price, \$3.50.

Biological and Clinical Chemistry. By MATTHEW STEEL, PH.D., Professor of Biochemistry in the Long Island College of Medicine, Brooklyn, N. Y. Pp. 770; 21 illustrations and 58 tables. Price, \$8.00.

The Medical Clinics of North America, Vol. 21, No. 5 (Baltimore Number, September, 1937). Pp. 318; 40 illustrations. Philadelphia, W. B. Saunders Company, 1937.

Prominent in this Baltimore number is a symposium of 10 articles on diseases of children. Hugh Young's article on the Prostate, Tillett's on the Serum Treatment of Pneumonia, Sprunt's on the Diagnosis of Liver Disease, Andrus' on Hypotension, and Wintrobe's on the Sedimentation Test will doubtless evoke especial interest.

The Roentgenologist in Court. By SAMUEL WRIGHT DONALDSON, A.B., M.D., F.A.C.R., St. Joseph's Mercy Hospital, Ann Arbor. Pp. 230. Springfield, Ill.: Charles C Thomas, 1937. Price, \$4.00.

Biological Time. By P. LECOMTE DU NOÛY, Chief of the Division of Molecular Biophysics, Pasteur Institute, Paris; formerly Associate Member of the Rockefeller Institute. With a Foreword by ALEXIS CARREL, M.D., Rockefeller Institute for Medical Research. Pp. 180; 31 illustrations. New York: The Macmillan Company, 1937. Price, \$2.00.

The Olfactory Mucosa as the Arena of Combat Against Poliomyelitis. By S. PESKIND, B.S., M.D., Cleveland, Ohio. Pp. 14. Cleveland: S. P. Mount Printing Company, 1937. (Price not given.)

An Outline of General Physiology. By L. V. HEILBRUNN, Associate Professor of Zoölogy in the University of Pennsylvania. Pp. 603; 122 illustrations. Philadelphia: W. B. Saunders Company, 1937. Price, \$5.00.

The Machinery of the Body. By ANTON J. CARLSON and VICTOR JOHNSON, The University of Chicago. Pp. 580; 187 illustrations. Chicago: The University of Chicago Press, 1937. Price, \$4.00.

Journal of Technical Methods and Bulletin of the International Association of Medical Museums, No. XVII. Editor: MAUDE E. ABBOTT, McGill University, Montreal; Associate Editor, ROBERT A. MOORE, Cornell University, New York. Pp. 208; illustrated. Toronto: International Association of Medical Museums, 1937. (No price given.)

This useful journal continues in this 1937 number its contributions to medical teaching, museum, photographic and histologic technique, and to pathology in general and cardiac anomalies in particular.

NEW EDITIONS.

Recent Advances in the Study of Rheumatism. By FREDERIC JOHN POYNTON, M.D., F.R.C.P. (LOND.), Consulting Physician, University College Hospital and the Hospital for Sick Children, Great Ormond Street, and BERNARD SCHLESINGER, M.A., M.D. (CAMB.), F.R.C.P. (LOND.), Physician to the Children's Department, Royal Northern Hospital; Physician to Out-patients, Hospital for Sick Children, Great Ormond Street. Pp. 380; 51 illustrations. Second edition. Philadelphia: P. Blakiston's Son & Co., Ltd., 1937. Price, \$5.00.

Neurology. A Most Comprehensive and Unified View of Modern Clinical Neurology. By ROY R. GRINKER, M.D., Chairman, the Department of Neuropsychiatry of the Michael Reese Hospital, Chicago; formerly Associate Professor of Neurology and Psychiatry, The University of Chicago. Pp. 999; 406 illustrations. Second edition. Springfield, Ill.: Charles C Thomas, 1937. Price, \$8.50.

External Diseases of the Eye. By DONALD T. ATKINSON, M.D., F.A.C.S., Consulting Ophthalmologist of the Santa Rosa Infirmary and the Nix Hospital, San Antonio, Texas; Fellow of the American Academy of Ophthalmology and Oto-Laryngology. Pp. 718; 494 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, \$8.00.

The Human Mind. By KARL A. MENNINGER. Pp. 517; illustrated. Second edition, corrected, enlarged and rewritten. New York: Alfred A. Knopf, 1937. Price, \$5.00.

Vitamins in Theory and Practice. By LESLIE J. HARRIS, Sc.D., D.Sc., Nutrition Laboratory, University of Cambridge, and Medical Research Council. Pp. 242; 66 illustrations and 44 tables. Second edition. Cambridge: The University Press, 1937. Price, \$3.00.

PROGRESS OF MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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AND

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INSULIN SHOCK THERAPY IN SCHIZOPHRENIA.

SCHIZOPHRENIA, one of the most serious problems of mental illness confronting medicine, affects between 30,000 to 40,000 individuals annually²⁹ and, by virtue of its impairment of normal adaptability to ordinary everyday environments, accounts for occupancy of about one-fifth of all hospital beds in the United States.¹⁶ Since most of these patients are supported by the State, any treatment which can increase the incidence of remissions in an ordinarily progressive habit deterioration is worthy of strongest consideration from the economic standpoint alone. From the standpoint of rendering a socially inadequate individual adequate, such a treatment should be conscientiously and critically undertaken.

Success of any therapy in schizophrenia is so often a measure of how early it is employed that early recognition of the condition is necessary. Essentially,²⁹ the schizophrenic reaction occurs in individuals who phylogenetically or ontogenetically are predisposed to meet poorly the various exigencies of life. There is not a matter of fact acceptance or rejection of various life situations with increasing maturity and integration from successive encounters; but rather a tendency towards regressiveness and withdrawal from important concrete situations and difficulties. This is often manifest in individuals by increasing seclusiveness, excessive day dreaming and phantasy formation, abnormal interests in religion and metaphysical subjects, grimacing or silliness with odd mannerisms and incongruities of behavior. There will often be peculiar attitudes toward self and body along with various unsupported hypochondriacal complaints and delusions and hallucinations. These individuals are often overly conscientious, idealistic, with a high sense of esthetic values, rendering the every day situations of family relationships, adolescence, school, marriage, and so on, too difficult to cope with.

The result is a progressive withdrawal from these realities into an unreal world of preoccupation, projection and phantasy.

Treatment has attempted to establish rapport⁸ and, through a process of reëducation and reorientation, to modify the individuals various attitudes that have been incompatible with adjustment. Assets are utilized and liabilities rationalized and the development of new and healthier habit patterns of reaction is one of the main goals. In many cases, however, loss of contact with reality is so great as to negate many of the directional efforts of psychiatrists and the establishment of any rapprochement is difficult. Various agents have been tried to produce an increasing contact and a lessened confusion and distortion of thought content. Nearly all of the employed agents have enjoyed a certain vogue and with varying success in the hands of different workers. Among these are such methods as the use of sodium amytal³ intravenously with production of "normal lucid intervals" in catatonia varying from 4 to 14 hours, various forms of prolonged narcosis,⁷ CO₂ and O₂ administration,^{20,21} fever therapy with sulphur in oil²⁷ and convulsive therapy with metrazol.²² All of these treatments are associated with some sort of "shock" or threat to the individual.

Among the latest and most widely publicized forms of therapy is that introduced by Sakel^{25a} of Vienna. Following his successful use of insulin in combating withdrawal symptoms of morphinism^{25b} and the observation that there were some beneficial personality alterations following unavoidable hypoglycemic states, intentional hypoglycemic reactions were tried in schizophrenics.

The method outlined by Glueck¹¹ in this country is the one generally employed and no essential modifications have been made other than those arising out of adapting the treatment to meet unpredicted peculiarities in certain individuals. Arbitrarily, four phases are delineated but essentially the treatment consists of a progressive insulinization of the patient until coma is reached, then a series of coma-producing doses of insulin are given until the patient is seen to be benefited or not improved after a reasonable length of time. This is followed by small doses of insulin in recovered or improved cases until discharged.

Normally insulin is administered at 7.00 to 7.30 A.M., the patient being under basal conditions. The initial dose is 15 to 20 units intramuscularly or subcutaneously⁴, increasing 5 to 10 units daily, 6 days a week until a coma producing dose is reached which varies from 30 to 450 units.^{25c} This is maintained for a general average of 30 but at times as high as 65⁴ shocks. The hypoglycemic state is interrupted 4 to 5 hours after the initial injection, sufficient insulin having been given to allow for 1 to 1½ hours of coma. With remission or improvement of the psychosis, the large doses of insulin are supplanted by small (20 to 40 units) daily doses with interruption in 2 hours. This continues for about 8 days. Termination is effected by giving 150 to 200 gm. of sugar in tea, water, or milk, the patient drinking the solution in the early stages but in the coma state the solution is administered by nasal tube. Hunt and Feldman¹⁷ find that the solution is more rapidly absorbed if well diluted and warmed. Facilities must be available for immediate treatment in cases of emergency,^{4,13} and such stimulants as caffeine, coramine, adrenalin, and carbogen may be necessary, as well as solutions of glucose for intravenous use with proper apparatus for

administration. All observers stress the need of attendants who are familiar with the procedure and physicians who understand fully the principles of insulin hypoglycemia.

The symptoms of hypoglycemia in the schizophrenic are essentially similar to normal patients¹⁹ and the descriptions of all observers correspond closely. An accurate and detailed study is that of von Angyal.¹ The usual symptoms become manifest in about one-half hour after injection by a slight drowsiness, sweating which may later become profuse, increased salivation, and acceleration of pulse rate with a rise in systolic blood pressure up to 60 mm. and a slight fall in diastolic. The ordinary shock is "wet" in type. Dry shocks in which there is no increased perspiration are regarded as ominous. As the hypoglycemia progresses, various manifestations of disturbances of the nervous system are seen. Muscular twitchings, clonic in nature appear about the face and neck, usually just before passing into coma. At times, athetoid movements and attitudes of decerebrate rigidity appear. In the coma stage normal reflexes are diminished or abolished with pathologic reflexes present such as the Babinski, Oppenheim, Rossalimo, Gordon, and others. At times, transient hemiplegias or monoplegias are seen. In deepest coma all reflex activity is abolished.

More marked and serious manifestations demanding intervention are pulse rates above 150 or below 40, vasomotor collapse, epileptiform convulsions, extreme excitement, at times accompanied by terrific hunger, severe spasm of the larynx, Cheyne-Stokes respiration and abnormally low temperatures. These latter severe manifestations are not common.

Various interesting physiologic and biochemical observations have been made. Usually the temperature drops during the shock period. Bychowski, *et al.*⁴ report one of 32.2° C. In the afternoon there is at times a slight elevation. All observers note no relationship between blood sugar level and onset of coma. Kepler and Moersch¹⁹ state that the symptoms of hypoglycemia are dependent more on the rapidity of change in the concentration of the blood sugar than on the actual amount of sugar in the blood. The blood sugar at times drops to levels below the point of accurate estimation. Electrocardiograms show slight and apparently reversible alterations, chiefly depressions of the *T* waves.⁶ Hadorn¹⁴ studied electrocardiograms on 100 patients and found changes in two-thirds similar to those found in myocardial infarction and coronary sclerosis; lowering of the *S-T* interval and lowering and negative values of the *T* wave. The changes are usually reversible and he feels they are due to an altered biochemical state, from hypoglycemia and hyperadrenalism, rather than to actual lesions. He states that the question of late effects is yet to be answered. Significant electroencephalographic changes have been noted by Hoagland, Cameron, and Rubin.¹⁵ The pathologic picture is not clear as yet. Schmid²⁶ produced repeated hypoglycemic shocks in rabbits, attempting to simulate Sakel's treatment of humans. He found only minimal changes and thought these due to excess adrenalin which is increased in the blood by insulin injection. He states that he could not confirm the results of Stief and Tokay²⁸ who found definite cellular lesions in the brain following severe hypoglycemic shock. Grayzell¹² also produced hypoglycemic shocks in rabbits and concluded that convulsions were neces-

sary to produce cerebral lesions and the greater the number and severity the more marked the changes, consisting of shrunken cells, hyperchromasia, and corkscrewing of processes and zones of necrobiosis. Baker and Lufkin² in 3 patients who died of hypoglycemia found new and old hemorrhages in the brain. On 6 rabbits subjected to repeated convulsions no significant alterations were found. More work is needed. Forstmeyer¹⁰ found no significant alterations in the hematoencephalic barrier to bromide. There is a large amount of additional work being undertaken at present which may throw light on the problem of hypoglycemia. All investigators have noticed individual differences in susceptibility to insulin and some individuals are extremely resistant to usual coma producing doses. In others, there may be a hypoglycemic reaction as long as 7 hours after termination,⁵ particularly if some of the administered sugar is lost through vomiting.

Psychiatrically, the patient may manifest a variety of behavior from a drowsiness that gradually merges into coma to periods of acute and violent excitement. Often during shock there is an exaggeration of the psychosis with an increased manifestation and intensity of content. Delusions or hallucinations may become more manifest or the patient may whistle, sing, yell, moan and grimace, often making sucking movements of the lips. There is an amnesia for most of the events of the morning. At times, there may be short periods of comparative lucidity before the patient becomes comatose. Most observers in addition have noted that following termination of the shock, the patient is often in a peculiar state of suggestibility and communicability. However, attempts at any searching psychotherapy are discouraged, and, in general, the environment is made as neutral and tranquil as possible. Behavior following termination of treatment tends to correspond to that manifested at the time of interruption and this is utilized therapeutically. Cameron and Hoskins⁵ have found that in paranoid patients best results are obtained when deep coma has been allowed to develop. In excited cases, termination after a few minutes of light coma, and in stuporous cases, termination during the precoma stage, so as to effect an activation of the individual. This view is in general accord with others.

Favorable cases gradually improve, their behavior becoming less bizarre, their preoccupation less and interest more. Delusions and hallucinations lose their intensity and finally disappear and insight may develop. Sakel^{25d} states "the hypoglycemic state weakens, inhibits and finally represses that portion of the mind which happens to be most active at the time, so that the hitherto latent subdued and repressed elements are again brought to the surface so that they can again prevail over those which are repressed. . . . In cases which run a favorable course, the repeated hypoglycemic states finally eliminate the psychosis so that the normal personality can again achieve complete dominance."

Various theoretical formulations have been advanced, all tentatively. Sakel^{25e} feels that the effectiveness of the hypoglycemic insulin treatment is due to the action of the insulin directly on the nerve itself. He feels that in schizophrenia products of the adrenal system excessively sensitize the cells of the nervous system so that normal adequate stimuli produce pathologic effects. In addition, phylogenetically ancient and

infantile nerve pathway patterns are revived, interfering with each other and producing an "intrapsychic ataxia." Insulin opposes the action of the "circulating hormone" so that excessive stimuli are muffled and the cells kept quiescent to the benefit of the individual, while the shock shatters the abnormal nerve pathways and allows the normal to again take precedence.

Glueck¹¹ feels that while the approach is biochemical, it is in no sense a strictly causal therapy. He is impressed with the radical generalized disturbance of vegetative, neurologic and psychic integration and a certain orderliness of manifestations in emergence from the hypoglycemic state that is meaningful and from the psychic standpoint suggest an increasing settlement of organismal and personality problems with a more specific reorientation to reality. Jelliffe¹⁸ offers an interesting psychoanalytic interpretation. Guirard and Nodet,¹³ after mentioning other shock therapies, feel that the insulin method is essentially one of shock calling forth a vital defense of the organism which effects improvement. Many observers feel that the insulin therapy of the psychoses is simply another form of shock therapy *per se* but one par excellence.

The results of treatment are very interesting. Most of the larger series are from the European investigators who report full remission rates up to 70.7% in early cases and up to 88% when the percentages of good remissions are added.^{9,23,25d} In older cases the percentage of remission or improvement is lower but considerably above the expected remission rate of 20 to 30% in all cases, up to 50% in acute cases and 10% in old.³¹ In the United States the percentages are lower but no large series of cases have been reported and it is too early to draw conclusions from comparative statistics.

The evaluation of results presents a problem. Rymer, Benjamin and Ebaugh²⁴ emphasize the need for a satisfactory method of qualitatively estimating results, feeling that more precise methods are needed. Thomas³⁰ asks for a settlement of the preliminary question of what one includes under the diagnosis of schizophrenia before attempting to evaluate results. Sakel^{25d} defines a full remission as present when "the patient is not only symptom free . . . but has full insight into his illness . . . normal emotional reactions and that he can return to his former work." "Good" remissions represent a condition in which the patient is free of schizophrenic symptoms, but has a slight degree of defect. And finally, he speaks of social remissions in which there is improvement but symptoms persist in part. In general, these are the criteria which have been used. As any change of behavior in patients will be interpreted in the light of the observer's concepts of the disease, and as there are admitted differences in various schools of psychiatry, this aspect of the problem needs further elucidation.

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REFERENCES.

- (1.) von Angyal, L.: *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 157, 35, 1937. (2.) Baker, A. B., and Lufkin, N. H.: *Arch. Path.*, 23, 190, 1937. (3.) Bleckwenn, W. J.: *Assn. for Res. in Nerv. and Ment. Dis.*, 10, 224, Baltimore, The Williams & Wilkins Company, 1931. (4.) Bychowski, G., Kaczynski, M., Konopka, C., and Szcztyt, K.: *Encephale*, 32, 17, 1937. (5.) Cameron, D. E., and Hoskins, R. G.:

- Schweiz. Arch. f. Neurol. u. Psychiat., 39, 180, 1937. (6.) de Chatel, A., and Palisa, C. H.: Klin. Wehnschr., 14, 1784, 1935. (7.) Cloetta, M., and Maier, H. W.: Am. J. Psychiat., 91, 1409, 1935. (8.) Diethelm, O.: Treatment in Psychiatry, New York, The Macmillan Company, 1936. (9.) Dussik, K. T., and Sakel, M.: Ztschr. f. d. ges. Neurol. u. Psychiat., 155, 351, 1936. (10.) Forstmeier, W. M.: Schweiz. Arch. f. Neurol. u. Psychiat., 39, 95, 1937. (11.) Glueck, B.: New York State J. Med., 36, 1, 1936. (12.) Grayzell, D. M.: Arch. Int. Med., 54, 694, 1934. (13.) Guirard, P., and Nodet, C.-H.: Ann. Med.-psychol., 94, 670, 1936. (14.) Hadorn, W.: Schweiz. Arch. f. Neurol. u. Psychiat., 39, 64, 1937. (15.) Hoagland, H., Cameron, D. E., and Rubin, M. A.: Am. J. Psychiat., 94, 183, 1937. (16.) Hoskins, R. G.: J. Am. Med. Assn., 96, 1209, 1931. (17.) Hunt, R. C., and Feldman, H.: Ibid., 109, 1119, 1937. (18.) Jelliffe, S. E.: J. Nerv. and Ment. Dis., 85, 575, 1937. (19.) Kepler, E. J., and Moersch, F. P.: Am. J. Psychiat., 94, 89, 1937. (20.) Loevenhart, A. S., Lorenz, W. F., and Waters, R. M.: J. Am. Med. Assn., 92, 880, 1929. (21.) Loevenhart, A. S., Lorenz, W. F., Martin, H. G., and Malone, I. Y.: Arch. Int. Med., 21, 109, 1918. (22.) Meduna, L.: Psychiat.-neurol. Wehnschr., 37, 317, 1935. (23.) Muller, M.: Schweiz. Arch. f. Neurol. u. Psychiat., 39, 9, 1937. (24.) Rymer, C. A., Benjamin, J. D., and Ebaugh, F. G.: The Hypoglycemic Treatment of Schizophrenia, J. Am. Med. Assn., 109, 1249, 1937. (25.) Sakel, M.: (a) Neue Behandlungsmethode der Schizophrenie, M. Perles, Vienna, 1935; (b) Deut. med. Wehnschr., 42, 1777, 1930; (c) Am. J. Psychiat., 94, 111, 1937; (d) J. Nerv. and Ment. Dis., 85, 561, 1937; (e) Am. J. Psychiat., 93, 829, 1937. (26.) Schmid, M. H.: Ann. Med.-psychol., 94, 658, 1936. (27.) Shapiro, L. B., and Read, C. F.: J. Nerv. and Ment. Dis., 86, 162, 1937. (28.) Stief, A., and Tokay, L.: Ztschr. f. d. ges. Neurol. u. Psychiat., 139, 434, 1932. (29.) Strecker, E. A., and Ebaugh, F. G.: Practical Clinical Psychiatry, 4th Ed., Philadelphia, P. Blakiston's Son & Co., 1935. (30.) Thomas, J. M.: New England J. Med., 217, 356, 1937. (31.) Wilson, I. G. H.: Quoted by Morse, R. T.: J. Kansas, Med. Soc., 38, 248, 1937.

OTO-RHINO-LARYNGOLOGY.

UNDER THE CHARGE OF

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RECENT ADVANCES IN PARANASAL SINUS DISEASE.

THERE is a continuously increasing interest in paranasal sinus disease if one is to judge by the large number of contributions that persist in appearing in the literature. The general tone indicates that the pendulum is swinging away from the pessimistic point of view and that a better appreciation of the functional activity of the ciliary mechanism of the mucous membranes offers a more hopeful outlook in its response to therapy. The skepticism on the part of the profession in regard to the curability is also shared by the laity and as both Black⁸ and Zwerling¹⁰⁶ state, the patient as a rule is convinced that sinus conditions are attended by prolonged treatment, repeated operations with tedious after care and but little hope for cure. This attitude on the part of the public has not been an unmitigated evil, for it has had its rôle in guiding our attempts at therapy, both medical and surgical, in more conservative paths.

Etiology. There is an increasing appreciation of the basic rôle played by allergy in the production and maintenance of chronic sinus disease. This has been covered in detail by us in a recent review. In a review of 13 cases of asthma in which the maxillary sinuses were operated upon, De Stio²⁴ came to the conclusion that the poor results encountered were due to the fact that the asthma and the sinus condition were both the results of the allergic state of the patient and that the surgery would have but little influence upon the underlying allergic factor. Kelley⁵¹ found Roentgen ray evidence of sinus disease in 89 of 100 cases of asthma that he studied. Irrigations of the sinuses rarely revealed true pus but most frequently globular masses of mucoid material. Puff⁸¹ describes the presence of eosinophils in the nasal secretions as an indication of an allergic status. McCready⁶⁷ could also demonstrate sinus disease in 85 % of several hundred asthmatic patients. Podesta,⁷³ in a review of the subject, also stresses the allergic nature of many cases of sinusitis. The rôle of heredity in the incidence of sinus disease is stressed by Ridpath⁸⁶ who has found sinus disease in every member and in two generations of certain families. Wood¹⁰³ feels that our method of blowing our noses might be responsible for most sinus infections. He states that tissue resistance in the nose proper is high and that in forcibly blowing our noses we tend to project the infectious secretions into the sinuses where the defensive mechanism is relatively low. He advises sniffing the secretions back into the throat along the same path the ciliary mechanism would sweep it physiologically. That blowing the nose in acute rhinitic states has frequently resulted in the production of an acute otitis media by insufflation *via* the Eustachian tube into the middle ear is an accepted fact, so Wood's assumption is not illogical. Dust-laden air as a factor in the production of sinus disease is described by Rhodes⁸³ who found an increased incidence in sinus disease resulting from severe dust storms in the dust bowl areas of several western states. In a review of 172 cases of antral disease Jankowski⁴⁸ was able to attribute 69 % to influenza and Iwata⁴⁶ reported 2 cases of scarlet fever complicated by sinus disease. Cullom¹⁹ believes that sinuses infected in the course of a contagious disease retain a chronic and frequently latent infection. He observed sinusitis present in 91 % of cases of scarlet fever in which otitis media had developed. The sinus infection as a rule was on the same side as the involved ear. In a study of the bacteriologic findings in chronic maxillary sinusitis Enlows and Alexander²⁹ found the streptococcus pyogenes in 9 %. The staphylococcus, both hemolytic and non-hemolytic, was found in over 70 % of 64 cases by Woodward.¹⁰⁴

Relation to Pulmonary Disease. The route of infection from the paranasal sinuses to the pulmonary tissues was studied by Larsell and Fenton⁵⁷ by injecting dyes into the mucosa of the frontal sinus and pharynx and following the path of the material into the lung. They found the dye to be carried into the sinus lymph spaces and lymphatics, the retropharyngeal and deep cervical lymph nodes, cervical lymphatics, subclavian vein, superior vena cava, the right side of the heart and the pulmonary capillaries.

Bronchiectasis is well known to be associated with chronic sinus disease. Watkins¹⁰² finds that it is quite the exception to find bronchiectasis without sinusitis and claims that early diagnosis and treatment of

the sinus condition in the presence of a chronic cough will prevent its occurrence. He found the sinuses involved in 89 % of 56 cases of bronchiectasis. In a series of 70 cases of bronchiectasis Kartagener and Ulrich⁶⁰ found sinus disease to be present in 56 %. Leon-Kindberg and Blinder⁶¹ report an interesting case of tuberculosis that was activated by the development of a pulmonary abscess as a complication to an acute rhinitis and maxillary sinusitis.

Arthritis. Littell⁶⁴ found a definite relationship between sinus infection and arthritis in 20 cases that he observed. He noted that the history frequently revealed that the arthritis had its onset at the time of an acute upper respiratory infection. He was able to effect improvement in 18 of his cases.

Bacteremia. In 90 cases of complications of acute sinus disease, such as meningitis, cavernous sinus thrombosis, brain abscess, and osteomyelitis, Goldman³⁶ found 44 % of cultures taken in 37 cases to show organisms. He advises routine blood cultures in acute sinus disease as an aid in prognosticating a complication.

Diagnosis. The importance of local findings of boggiess of the nasal mucosa, and edema and swelling in and about the middle turbinate and meatus is stressed by Harper⁴⁰ in discussing hidden infections of the sinuses. He observes that not infrequently the Roentgen ray and transillumination of the sinuses may afford little, if any, evidence of sinus involvement. The value of roentgenograms in diagnosing frontal sinus disease is expressed by Lumsden,⁶⁵ although he admits that the degree of involvement cannot always be accurately determined. The accuracy of radiologic findings in antral disease was studied by Shannon⁹² who compared the Roentgen ray findings with the condition noted at operation in 296 patients. In 130 cases in which a thickened membrane was found at operation this fact was diagnosed in the pre-operative films. Polypi were diagnosed in 106 cases and were found at operation, and similar corroborative findings in 22 cases with a pre-operative diagnosis of frank pus. Such a high coefficient of accuracy undoubtedly led the author to state that iodized oils as a contrast media were but rarely necessary. Ribbing⁸⁴ also states that there need be no difficulty in determining differences in mucosal thickness and polypi in sinuses free from fluid and that contrast media are superfluous. Barmwater,⁷ however, is an ardent advocate in the use of contrast media and cites a number of illustrative cases. Mittermaier⁷¹ also advocates the use of contrast media. In a study of transillumination Richards⁸⁵ has devised a method in which the element of human fallibility in judging or interpreting the degree of impairment of transillumination may be overcome by substituting a photoelectric cell for the human eye and taking direct readings from a meter. Experimentally, it was found to be superior to the roentgenogram in differentiating between varying degrees of opacity in various mixtures of pus and serum.

Effler²⁷ has arrived at the conclusion that the gross appearance of the irrigated material from a sinus may give some information as to the infective organism. The appearance of solid mucoid clumps in otherwise clear solutions in acute cases presaged recovery. A cloudy yellowish discharge was found to indicate a *Staphylococcus aureus* infection, while a cloudy white discharge indicated a *Staphylococcus albus* infection. A greenish tinge to the fluid was given by the presence of *Bacillus*

pyocyaneus, while the *Bacillus proteus* was associated with foul odor. Granular scanty blood tinged irrigates indicated streptococcic involvement. In chronic antral infections he found two typical irrigates; one in which slight shreds and flakes in an otherwise clear solution, indicating a mild lesion that tends to recover with conservative measures; the other, a milky, foul-odored irrigate, indicating mucosal degeneration and polypi, requiring surgical intervention for relief.

In a study of the sedimentation rate in 30 patients with chronic sinus disease, Lintz⁶³ found but 2 in which the rate exceeded the normal and rightfully concluded that it was of no diagnostic or prognostic value.

Treatment. An increasing appreciation of the functional activity of the ciliated epithelium has inspired an attitude of conservatism in surgical, as well as in non-surgical measures, employed in the treatment of sinus disease. Proetz⁸⁰ advises ephedrine in saline solution in acute nasal infections and isotonic solutions in sinus irrigation as having the least objectional effect upon the ciliated epithelium. He also discourages the use of oily solutions as he finds that they interfere with the normal action of the cilia and the mucous blanket. The use of mild shrinkage medicants in association with mild organic silver preparations continue to be advocated by Ashley⁵ using a 0.25 % neo-synephrin and a 5 % neo-silvol solution. Crebbin¹⁸ also recommended the use of neo-synephrin but advocated the use of a tampon of a 40 % solution of neo-silvol. Black,⁸ in addition to using tampons of 0.25 % neo-synephrin, uses neo-silvol in a concentration of but 10 %, which is more common practice. Fitzhugh⁸¹ found neo-synephrin in a concentration of 0.5 to 1 % to be more effective than ephedrine, and in addition it exhibited milder constitutional effects.

The use of bacterial antigens also have their advocates. In an experience extending over a period of 3 years with the d'Herelle type of bacteriophage, Ruskin⁸⁷ found it to be of value in decreasing the frequency of acute attacks. The bacteriophage was applied by tampons, nasal spray, and by instillation in the form of drops. Gundrum⁸⁷ was able to improve 32 of 36 patients with chronic sinusitis by the use of a bacterial antigen in combination with a dilute solution of neo-synephrin. He begins with the application of a 10 % concentration of the antigen and gradually increases it to 100 %. In a series of 62 patients treated with Krueger's bacterial antigen over a period of 3 years, Kracaw⁵⁵ observed a cure or great improvement in 52 cases. The treatment must be carried out over a period of 4 or more months. Kelly⁵² also reports good results in the use of the Krueger vaccine. Fox and Harned⁴³ report on a novel extract of the nasal mucosa of hogs in the treatment of sinus infections. They believe that the extract gives some promise when used both orally and hypodermically.

Physical methods in the treatment of sinus disease continue to receive attention. The efficacy of various means of applying heat to the sinuses were studied by Andreen and Osborne³ who introduced a thermocouple into the antrum and recorded the effects of the heat inducing modalities. The increase of the most efficient, showed but an unimpressive increase from an initial 98.2 and 98.5 to 99.1° F. In order of efficiency are electromagnetic field and diathermy, thermospectral lamp, Cutler water cooled lamp, compsolite, short wave diathermy and Elliott apparatus. Bryant¹⁰ has found the Elliott apparatus of value in acute

cases but of little benefit in chronic cases. The method consists of the introduction into the nose of closed rubber tubes connected with a heating apparatus that causes the hot water to circulate through the tubes. Treatment is started with the temperature of the water at 120° F. and increased to 130° F. May⁶⁹ advises the use of the water cooled mercury lamp applied to the nose by a quartz nasal applicator, in association with infra-red therapy and short wave diathermy, in the treatment of antral infections, and Stein⁹⁶ also advocates the use of infra-red rays, diathermy and short wave as conservative measures in the treatment of acute and chronic sinus infections. Haslinger⁴¹ also recommends light therapy in association with sweat baths. The Roentgen ray was successfully used in obtaining relief in 8 of 10 cases of acute frontal sinusitis by Lazarovits.⁵⁹ But one treatment was found necessary, applying a $\frac{1}{2}$ unit skin dose.

Proetz Displacement Therapy. The use of Proetz's method of displacement therapy of the sphenoid and ethmoid sinuses continues to receive deserved attention. Laskiewicz⁵⁸ advises its routine use in the treatment of sinus disease in children and Parkinson⁷⁵ also favors its employment. The Proetz treatment given at 4- and 5-day intervals was found to be especially effective by Arslanian and Valette,⁴ particularly in children. They report 15 cases with good results in all. Shambaugh⁹¹ states that chronic ethmoiditis sometimes responds to repeated evacuation by displacement technique and Ridpath⁸⁶ found the method adequate in a case of frontal sinusitis. Shuster and Schuster⁹³ point out that displacement should only be used in receding stages of an acute infection. In a discussion of the value of the method Davis²² finds that it must be used several times a week over a period of time to be effective. Nasal larvæ have been evacuated from the sinuses by Proetz displacement. Caldas¹³ reports 3 cases in which he uses iodoformed paraffin oil in a concentration of 5% and Liggett⁶² employed it in a similar manner for nasal larvæ. Kracaw⁵⁵ has utilized the Krueger vaccine by this method with success. Laskiewicz⁵⁸ used the antiviral by this means in treating ethmoiditis and found the infection to clear in from 3 to 5 days. Gundrum and Seminov³⁸ describe the results in 150 cases with definite improvement in 52%. In 16 refractory cases some improvement was noted in 11 by the addition of a stock bacterial antigen filtrate. In an additional 135 cases treated with the stock antigen in addition to ephedrine from the very onset of the treatment, improvement was noted in 64%.

Sinus Irrigation. Sinus irrigation or lavage is one of the simpler methods of treating suppuration in the antra, sphenoid or to a lesser extent the frontal sinuses. The sinuses mentioned may be entered through their natural ostia or, in the case of the antrum or sphenoid, may be perforated by a suitable trocar. In a study of the maxillary ostium in 163 adult skulls, Van Alyea¹⁰⁰ found that the natural orifice was easily cannulated in some 55% so that antral puncture is only necessary in about one-half of all patients seen. Sinus irrigation was able to effect a cure in 66% of 178 patients of antral disease treated by Miller.⁷⁰ Moore⁷² also describes several cases relieved by irrigation. In a review of 10 years' experience at the University Clinic at Budapest, Ipolyi⁴⁵ reports that 65% of 1413 cases of antrum disease was cured by irrigation alone. Muller dos Reis⁷⁴ once more calls attention to the

accidents that may attend an antral puncture. Complications such as paralysis, amaurosis, convulsions and syncope may follow air embolism caused by the pernicious practice of expelling the irrigating fluid from the antrum by a blast of air. It is far safer to permit the ciliary mechanism and the absorptive powers of the mucosa to care for the remaining fluid than chance such a grave complication.

Surgery. By far the largest number of contributions deal with the surgical treatment of sinusitis, and mainly in the technical aspects of most interest to the operating rhinologist. For that reason many papers dealing with technical aspects of surgery will receive little or no mention in this review.

In a discussion of the indications for surgery of the antrum, Ipolyi⁴⁵ advised conservative irrigation for a period of some 6 weeks, unless the suppuration was secondary to dental sepsis, osteomyelitis of the maxilla, new growth or foreign body. By this means 65% of 1413 cases observed over a period of 10 years could be cured. This agrees well with the common experience of most rhinologists who, as a rule, consider failure of irrigation to effect a cure over a period of time as a necessary preliminary before employing more radical surgery. If irrigation fails, then an intranasal antrostomy, or window placed in the inferior meatus for better ventilation and drainage must be considered. Ipolyi found this to be necessary in 23% of the cases which were cured. Miller⁷⁰ states that in chronic infections of the antrum, ventilation and drainage are impaired due to closure of the natural ostia. He feels that the drainage of the purulent sinus secretions by gravity through the dependently placed window and reestablishment of ventilation will permit most antral linings to recover unless grossly polypoid and diseased. Alteri² also feels that in many cases of chronic antrum infection the mucosa and ciliary function may return to normal if adequate drainage is provided by a large window placed in the inferior meatus. Hoover⁴³ advises an opening in the inferior meatus for better drainage and ventilation if the progress is unsatisfactory. He advises radical operation if the mucosa is polypoid or cystic. That the presence of marked polypoid, cystic and degenerated mucosa or that affected with other irreversible change in all probability would be but little influenced by an intranasal antrostomy, is born out by King⁵³ who checked the end results of 14 cases of antrum disease treated by that method. In the 5 cases in which no clinical improvement was noted postoperative examination with the Roentgen ray, utilizing contrast media, disclosed pathologic tissue. He concludes that the failure of the operation was due to the irreversible pathologic tissue.

Sinus infections with tissue changes such as these require the removal of the pathologic tissue from within the sinus before a cure may be expected. This is accomplished by a sublabial antrum operation of the Caldwell-Luc type or some modification. After removal there is a complete regeneration of the mucosa. Brownell⁹ reviewed the clinical and experimental work on the regeneration of the mucosa and concludes that a complete regeneration may be expected after a period of 3 to 5 months has elapsed. The new mucosal lining is complete including ciliated epithelium. Good results may, therefore, be reasonably expected from the Caldwell-Luc procedure and Syme⁹⁷ accordingly reports that 65 of 77 patients who underwent this procedure reported

excellent results. Ipolyi⁴⁵ reports good results in all cases operated upon by the radical method. Sewall,⁹⁰ however, reports a number of recurrences with the radical operation and finds the recurrence to be due to cyst formation, partial obliteration and walled off abscesses in the sinus. He advocates keeping the opening patent so that the cavity may be observed and cleansed until complete epithelialization has occurred.

During the performance of the radical operation some of the nerves comprising the dental loops distributed to the teeth may be traumatized and there have been many reports of dental difficulty as a result of the operation. Schmidt,⁸⁹ however, in an examination of the teeth of 45 patients who had undergone 63 operations, was unable to determine any increase in sensory disturbances or in the incidence of caries. In a total of 425 teeth examined by electrical tests, but 10.8% showed prolonged anesthesia and only 2 necrosis of the root. In a similar study of the teeth with electric currents, Dahm²⁹ found complete anesthesia up to 6 months and hyposthesia up to 9 months. Both Dahm and Schmidt note that the state of anesthesia is in no way related to the vitality of the tooth, which is dependent on its blood supply. While damage to the dental nerves may not be entirely avoided, they may be reduced to a minimum by following the suggestion of Ehrhardt²⁸ who advises a high incision and removal of as little bone as possible when approaching the floor of the antrum along the facial wall.

The External Fronto-ethmo Sphenoid Operation. The conceded poor results following intranasal surgery of chronic polypoid and suppurative disease of the ethmoid, sphenoid, and frontal sinus has caused renewed interest in various types of radical operations from an external approach upon these sinuses. There continue to appear a large number of papers bearing mainly on the technical aspects of the Lynch, Ferris Smith, or Sewall types of the external ethmo-spheno-frontal operation. The whole consensus of opinion is in agreement with Futch³⁴ who advises a thorough trial of all less radical measures before resorting to this rather formidable procedure. He found that 4 of 6 patients with asthma evidenced improvement and 4 allergic patients were also definitely benefited. Bryant¹⁰ reports good results in 28 cases. He performed these upon patients with extensive involvement in which there was a failure after intranasal surgery. He noted the occurrence of 3 cases of diplopia, lasting from 1 to 3 months. Wagner¹⁰¹ and Daito²¹ also favor the procedure and McNaught⁶⁸ admits that the radical operation may fail through the constriction of the naso-frontal opening and through the presence of pathologically involved peri-orbital ethmoid cells. Finally, Proetz⁸⁰ cautions against operations of this type that throw the sinuses into the general nasal cavity as the effect of too much air in desiccating the delicate ciliated epithelial lining. Luongo,⁶⁶ Howarth,⁴⁴ and McNaught⁶⁸ give excellent presentations of the technical execution of the operation and Yates¹⁰⁵ describes a skin incision that minimizes the resultant scar.

Intracranial Complications. Meningitis. In an extensive and thorough presentation of the subject of the pathways of infection in rhinogenic meningitis, Jacobsgaard⁴⁷ reports on the histologic examination of tissues of patients dying of a rhinogenic meningitis in whom no nasal operation was performed, thus leaving tissue for study intact. He found that the perineural lymphatics of the olfactory nerves and

localized osteomyelitis of the sinus structures contiguous with dura were the two important means of transmission. More light as to the possible rôle of the lymphatics of the frontal sinus in the extension of infection into the cranial cavity has been thrown by the work of Chiara and his associates¹⁵ who were able to demonstrate the diffusion of colloidal thorium from the frontal sinuses to the meninges, the sulci, and the convolutions of the brain by both histologic and radiologic studies. Kramer and Som⁵⁶ report 10 cases of meningitis secondary to sphenoid infection. Pain in the occiput radiating to the temples and down the spine and the positive result of a sphenoid sinus irrigation aid in establishing the etiologic diagnosis of the meningitis. The authors advise intranasal exenteration of the affected sinus. Four cases recovered, 3 spontaneously and 1 after surgery. As the spinal fluid count in the recovered cases was never high, and no bacteria could be demonstrated a true diagnosis of suppurative meningitis in these cases could not be maintained. In the other cases reported bacteria were found in the spinal fluid and were associated with the fatal outcome. Field and Rogers³⁰ report a child dying of a meningitis which at postmortem disclosed a suppurative sphenoiditis. A new method of drainage of the basal cistern by way of the palate and sphenoid in the treatment of meningitis is advocated by Smith.⁹⁴ He utilizes a drill in perforating through the sphenoid bone and exposing the dura, which is opened to drain the basal cisterna.

Brain Abscess. Two fatal cases of subdural abscess of the frontal lobe are reported by Courville.¹⁷ The preceding frontal sinus infection was undiagnosed in life and found at autopsy. The presence of contralateral Jacksonian attacks is a significant sign and should lead to the investigation of the sinuses as a possible source of the infection. Hoge⁴² reports 2 cases of brain abscess secondary to sinus infections after swimming. One case in which signs and symptoms of cerebral involvement were slow in appearance, after a period of a month, surgical drainage was followed by a cure. In the other case a rapid course was evident, which resulted in death. The slow progress of the recovered case undoubtedly permitted encapsulation of the abscess to occur, with resultant success in drainage. Atauz and Dodds⁶ report a slow developing rhinogenic frontal lobe abscess characterized by persistent headache and relative bradycardia. Surgical drainage was successful. Cavanaugh¹⁴ reports a case of frontal lobe abscess which was operated after a period of time and successfully drained. Piquet and Delcoux⁷⁷ report a fatal case of frontal lobe abscess in which death was caused by the presence of secondary daughter abscesses in spite of adequate drainage of the primary abscess.

Osteomyelitis. In a thorough consideration of the subject, including a histologic study of 3 cases, Mosher⁷³ found that the marrow spaces frequently contained small abscesses and that the infection spread by the way of the diploic veins and the inner surface of the bone. He found edema of the overlying soft tissues to be the most reliable guide as to the extent of the bony involvement and that it also antedates the appearance of Roentgen findings by several days. He advocates wide excision well into the healthy bone, Jones,⁴⁹ Podesta and Carrascossa,⁷⁹ and Alonso,¹ also report several cases of osteomyelitis recovering after radical wide excision recommended by Mosher. Two fatal cases are

reported by Delcoux, Patoir and Bedrine.²³ These preceding cases were mainly complications of suppurative frontal sinus disease and many gave a history of onset after swimming. Lennon⁶⁰ reviews 91 cases of osteomyelitis of the frontal bone gleaned from the literature, and finds that the staphylococcus is the most predominating organism. He found that young adults were mainly affected. He states that the infection travels by way of the diploë and is far in advance of the Roentgen findings. Clevenger¹⁶ reports a fatal case originating in the ethmoid sinuses and Tamura⁹⁸ reports 2 cases of osteomyelitis of the upper jaw in infants that manifested themselves clinically by swelling of the face and eyelids. Recovery followed incision with removal of the sequestrum.

Ocular Complications. Snellman,⁹⁵ in a review of sinus infections observed at the University of Helsingfors over a period of 10 years, found an incidence of orbital complications in 3%. Periostitis and subperiosteal abscess were the most frequent, and the most common offending sinus was the ethmoid. The infective organism in most cases was the streptococcus. The treatment consisted in incision and evacuation of the abscess and opening of the offending sinus. The periostitis was treated successfully by conservative measures. An extensive study of the anatomical and general findings in rhinogenic orbital disease was presented by Cordierlein, Coulouma and Van Varseveld.¹² They classify the various complications as those arising from the anterior group of sinuses producing lid inflammations, dacryocystitis, phlegmon and muscular paresis; those arising from the posterior group producing optic neuritis, ocular nerve palsies of the third, fourth and sixth nerve, and neuralgias of the sphenopalatine or trigeminal nerve. Sargnon⁸⁸ similarly describes anterior or palpebral complications of the orbit and states that they are rather benign, superficial, arising from acute fronto-ethmoid infections, yielding to a palliative management or simple external incision. The posterior or retro-orbital infections are deep seated and more serious and require surgical intervention. In a series of 38 cases of orbital infection reviewed by Burger¹¹ there was recovery in 35 and 3 deaths due to meningitis in 2 cases and brain abscess in the remaining one. He notes the tendency for spontaneous regression in young children. A number of authors, among them Djacos,²⁵ Flachs,³² and Terrien⁹⁹ report similar cases.

There is a large number of contributions dealing with the relation of visual disturbances and retrobulbar neuritis as a consequence of sinus disease. As in past years many such cases have been reported in which there was recovery in vision following sinus surgery, in spite of the fact that evidence of lesions in a sinus was inconsequential or absent. In a case associated with poor vision, Halphen and Coussieu³⁹ were enabled to effect a return of visual function after opening the sphenoid and ethmoid sinuses in which no pathologic changes could be noted. He was unable to determine whether the restoration of vision was due to the effect of the local anesthesia, the relief of vascular stasis, by the bleeding attendant to the operation, or some other undetermined cause. Koch and McCready⁵⁴ feel that Roentgen evidence of slight haziness of the ethmo-sphenoid may indicate a hyperplasia which may be the cause of the visual disturbance. Rainey⁸² reports a case of rapidly developing blindness cured by sinus exenteration during which nothing but a congested mucosa was found. Persky,⁷⁶ Genet,³⁵ and Durando,²⁶ are

but a few of the many others that report similar experiences. The most common explanation of the effects is that it is due to local depletion by bloodletting, or improvement of circulation in the optic nerve by the use of the local anesthetic or increased aëration of the sinuses. In many cases in which failure of vision to return was noted, multiple sclerosis developed at some subsequent time.

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REFERENCES.

- (1.) Alonso, J. M.: *An. de oto-rinc-laring. d. Uruguay*, 5, 108, 1935. (2.) Alteri: *Morgagni*, 77, 1199, 1935. (3.) Andreen, M. A., and Osborne, S. L.: *Arch. Otolaryng.*, 24, 331, 1936. (4.) Arslanian, N., and Valette, M.: *Rev. de Laryng. de Bordeaux*, 55, 862, 1934. (5.) Ashley, R. E.: *Southwestern Med.*, 20, 349, 1936. (6.) Atauz, S. L., and Dodds, A.: *Rev. Asoc. med. argent.*, 49, 1827, 1935. (7.) Barmwater, K.: *Hals-Nasen u. Ohrenarz.*, 27, 5, 1936. (8.) Black, W. B.: *J. Missouri Med. Assn.*, 33, 260, 1936. (9.) Brownell, D. H.: *Arch. Otolaryng.*, 24, 753, 1936. (10.) Bryant, F. L.: *Laryngoscope*, 46, 853, 1936; *Minnesota Med.*, 19, 364, 1936. (11.) Burger, H.: *Nederl. tijdschr. v. geneesk.*, 80, 1180, 1936. (12.) Cordier, W., Coulouma, P., and Van Varseveld, F.: *Echo med. du Nord*, 5, 10, 1936. (13.) Caldas, S.: *Anais de Oto.-Rino-Larin.*, 2, 169, 1936. (14.) Cavanaugh, J. B.: *J. Laryng. and Otol.*, 51, 239, 1936. (15.) Chiara, G., Caponnetto, A., and Nicotra, A.: *Radiol. med.*, 22, 1092, 1935. (16.) Clevenger, W. F.: *Trans. Indiana Acad. Ophth. and Otolaryng.*, 20, 59, 1936. (17.) Courville, C. B.: *Bull. Los Angeles Neurol. Soc.*, 1, 55, 1936. (18.) Crebbin, J. T.: *Tri-State Med. J.*, 8, 1589, Feb., 1936. (19.) Cullom, M. M.: *Trans. Sect. Laryng. Otol. and Rhinol. Am. Med. Assn.*, p. 84, 1936. (20.) Dahm, H.: *Deut. Zahnheilk.*, 3, 395, 1936. (21.) Daito, T.: *Arch. f. Ohren-, Nasen- u. Kehlkopf.*, 139, 300, 1935. (22.) Davis, T. C.: *Medical World*, 52, 106, 1934. (23.) Delcoux, P., Patoir, G., and Bedrine, H.: *J. de chir.*, 47, 232, 1936. (24.) De Stio, D. S.: *Arch. Otolaryng.*, 24, 606, 1936. (25.) Djacos, M. C.: *Bull. Soc. d'opht. de Paris*, p. 545, June, 1936. (26.) Durando, F.: *Riv. oto-neuro-oftal.*, 12, 675, 1935. (27.) Effer, L. R.: *Laryngoscope*, 46, 848, 1936. (28.) Ehrhardt, E.: *Die Kieferhohlenoperationen unter besonderer Berücksichtigung der dentogenen Verhältnisse*, Dissert., Leipzig, 1935. (29.) Enlows, E. M. A., and Alexander, S. A.: *Arch. Otolaryng.*, 23, 665, 1936. (30.) Field, C. E., and Rogers, H.: *Bristol Med.-Chir. J.*, 53, 151, 1936. (31.) Fitzhugh, W. M., Jr.: *Arch. Otolaryng.*, 24, 425, 1936. (32.) Flachs, H.: *Folia ophth. orient.*, 2, 152, 1936. (33.) Fox, N., and Harned, J. W.: *Arch. Otolaryng.*, 24, 89, 1936. (34.) Futch, C. E.: *Surg., Gynec. and Obst.*, 62, 509, 1936. (35.) Genet, L.: *Bull. Soc. d'opht. de Paris*, pt. 2, p. 720, November, 1935. (36.) Goldman, J. L.: *Laryngoscope*, 46, 500, 1936. (37.) Gundrum, L. K.: *Arch. Pediat.*, 53, 287, 1936. (38.) Gundrum, L. K., and Seminov, H.: *Laryngoscope*, 45, 858, 1935. (39.) Halphen, E., and Coussieu, P.: *Rev. d'oto-neuro-ophth.*, 14, 198, 1936. (40.) Harper, J.: *Glasgow Med. J.*, 8, 1, 1936. (41.) Haslinger, F.: *Wien. klin. Wchnschr.*, 49, 1260, 1936. (42.) Hoge, T. R.: *West Virginia Med. J.*, 32, 564, 1936. (43.) Hoover, W. B.: *S. Clin. North America*, 15, 1603, 1935. (44.) Howarth, H.: *J. Laryng. and Otol.*, 51, 387, 1936. (45.) Ipolyi, F.: *Monatschr. f. Ohrenh.*, 70, 401, 1936. (46.) Iwata, I.: *Oto-rhino-laryng.*, 9, 319, 1936. (47.) Jacobsgaard, J.: *Ztschr. f. Laryng., Rhinol. Otol.*, 26, 387, 1936. (48.) Jankowski, W.: *Polska, gaz. lek.*, 15, 61, 79, 1936. (49.) Jones, A. C.: *Ann. Otol. Rhin. and Laryng.*, 45, 726, 1936. (50.) Kartagener, M., and Ulrich, K.: *Beitr. z. Klin. d. Tuberk.*, 86, 349, 1935. (51.) Kelley, S. F.: *Laryngoscope*, 46, 692, 1936. (52.) Kelly, J. D.: *Ann. Otol., Rhinol. and Laryng.*, 45, 1050, 1936. (53.) King, E.: *Ohio State Med. J.*, 32, 821, 1936. (54.) Koch, S. L., and McCready, J. H.: *Am. J. Roentgenol.*, 35, 215, 1936. (55.) Kracaw, F. C.: *Laryngoscope*, 46, 26, 1936. (56.) Kramer, R., and Som, M. L.: *Ibid.*, p. 507. (57.) Larsell, O., and Fenton, R. A.: *Arch. Otolaryng.*, 24, 696, 1936. (58.) Laskiewicz, A.: *Polski przegl. otol.*, 10, 179, 1935; *Ann. d'Oto-Laryng.*, p. 567, June, 1934. (59.) Lazarovits, L.: *Gyogyaszat*, 76, 309, 1936. (60.) Lennon, A. N.: *Laryngoscope*, 46, 754, 1936. (61.) Leon-Kindberg, M., and Blinder, H.: *Bull. et mém. Soc. méd. d. hôp. de Paris*, 52, 160, 1936. (62.) Liggett, H.: *J. Am. Med. Assn.*, 96, 1571, 1931. (63.) Lintz, R. M.: *J. Lab. and Clin. Med.*, 21, 1259, 1936. (64.) Littell, J. J.: *J. Indiana Med. Assn.*, 29, 270, 1936. (65.)

- Lumsden, R. B.: *J. Laryng. and Otol.*, 51, 230, 1936. (66.) Luongo, R.: *Laryngoscope*, 46, 1, 1936. (67.) McCready, J. H.: *West Virginia Med. J.*, 32, 404, 1936. (68.) McNaught, R. C.: *Arch. Otolaryng.*, 23, 544, 1936. (69.) May, F.: *Med. J. Australia*, 2, 495, 1936. (70.) Miller, A.: *Brit. Med. J.*, 1, 1299, 1936. (71.) Mittermaier, R.: *Hals-, Nasen- u. Ohrenarzt.*, 27, 2, 1936. (72.) Moore, J. H.: *West Virginia Med. J.*, 32, 410, 1936. (73.) Mosher, H. P.: *J. Am. Med. Assn.*, 107, 942, 1936. (74.) Muller dos Reis, W.: *Rev. oto-laring. de São Paulo*, 4, 135, 1936. (75.) Parkinson, S. M.: *Arch. Otolaryng.*, 23, 344, 1936. (76.) Persky, A. H.: *Med. Rec.*, 144, 364, 1936. (77.) Piquet, J., and Delcoux, P.: *Ann. d'oto-laryng.*, p. 185, February, 1936. (78.) Podesta, R.: *Rev. Asoc. med. argent.*, 49, 1540, 1935. (79.) Podesta, R., and Carascosa, A. E.: *Ibid.*, p. 1817. (80.) Proetz, A. W.: *Pennsylvania Med. J.*, 39, 385, 1936. (81.) Puff, F.: *Ueber die Aetiologie der polyposen Nasennebenhöhlen-erkrankungen*, Dissert., Köln, 1935. (82.) Rainey, J. J.: *Laryngoscope*, 46, 185, 1936. (83.) Rhodes, W. L.: *Med. Rec.*, 144, 363, 1936. (84.) Ribbing, S.: *Upsala lakaref. forh.*, 41, 369, 1935. (85.) Richards, L.: *Ann. Otol., Rhinol. and Laryng.*, 45, 307, 1936. (86.) Ridpath, R. F.: *Med. Times*, 64, 513, 1936; *The Eye, Ear, Nose, and Throat Monthly*, 15, 388, 1936. (87.) Ruskin, S. L.: *Laryngoscope*, 46, 107, 1936. (88.) Sargnon, A.: *Oto-Rhino-laryng. internat.*, 19, 721, 1935. (89.) Schmidt, G.: *Ztschr. f. Hals-, Nasen- u. Ohrenh.*, 39, 355, 1936. (90.) Sewall, E. C.: *Laryngoscope*, 46, 493, 1936. (91.) Shambaugh, G., Jr.: *Illinois Med. J.*, 69, 417, 1936. (92.) Shannon, E. H.: *J. Am. Med. Assn.*, 106, 599, 1936. (93.) Shuster, F. P., and Schuster, S. A.: *Southwest Med.*, 21, 44, 1937. (94.) Smith, F.: *J. Am. Med. Assn.*, 107, 189, 1936. (95.) Snellman, I.: *Duodecim*, 52, 811, 1936. (96.) Stein, S.: *Med. Rec.*, 144, 360, 1936. (97.) Syme, W. S.: *Glasgow Med. J.*, 126, 87, 1936. (98.) Tamura, I.: *Oto-rhinol-laryng.*, 9, 712, 1936. (99.) Terrien, F.: *Rev. gen. de clin. et de therap.*, 50, 705, 1936. (100.) Van Alyea, O. E.: *Arch. Otolaryng.*, 24, 553, 1936. (101.) Wagner, W. A.: *South. Med. J.*, 29, 9, 1936. (102.) Watkins, A. B. K.: *Med. J. Australia*, 2, 118, 1936. (103.) Wood, T. B.: *Med. Times*, 64, 516, 1936. (104.) Woodward, F. D.: *Arch. Otolaryng.*, 24, 753, 1936. (105.) Yates, A. L.: *J. Laryng. and Otol.*, 51, 715, 1936. (106.) Zwerling, S.: *Med. Times*, 64, 522, 1936.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 25, 1937.

A Simple Synthesis of Citrulline. ALTON C. KURTZ (Laboratory of Physiological Chemistry, University of Pennsylvania). A new and superior method has been developed which permits the synthesis of citrulline in good yields directly from ornithine without the tedious intermediate preparation of ornithuric acid, α -monobenzoyl ornithine and α -monobenzoyl citrulline. The method is based upon the ability of the cupric ion to mask the α -amino groups when chelate compounds are formed with ornithine and citrulline.

Ornithine monosulphate, easily obtained by the hydrolysis of α -carbamyl arginine, is converted into its copper complex. To a concentrated aqueous solution of this chelate compound an excess of urea is added and the mixture is heated in a sealed tube at 100° C. for several hours. The insoluble citrulline copper is precipitated. This is thereafter decomposed by hydrogen sulphide in the usual manner to give 65 to 71 per cent of the theoretical amount of citrulline, calculated from the ornithine monosulphate taken. The further use of chelate formation in organic syntheses is suggested.

Relative Effectiveness of Neutron Rays and Roentgen Rays on Various Cells of the Same Organism. R. E. ZIRKLE and I. LAMPE (Johnson Foundation, University of Pennsylvania, and Department of Radiology, University of Michigan). Earlier experiments* on the comparative effectiveness of neutron rays have shown: (a) That for at least some cells the effectiveness of the neutrons, per unit of tissue ionization, is greater than that of Roentgen rays; (b) that the relative effectiveness of the two radiations is sometimes quantitatively different from organism to organism.

The present experiments extend the observations to different cells of the *same* organism. The effectiveness of the neutrons relative to Roentgen rays is greater for *Drosophila* eggs 3.5 hours old than for similar eggs 1 hour old. Likewise, in studies on wheat seedlings, the neutron: Roentgen ray ratio of effectiveness is greater for the root than for the shoot. Therefore it can be concluded that the relative susceptibility of different cells in the same organism is not the same for neutron rays as for Roentgen rays.

The Double Innervation of Striated Muscle. JOHN B. GAYLOR (Marine Biological Laboratory, Woods' Hole, and Johnson Foundation and Institute of Neurology, University of Pennsylvania). Opinion is divided as to the presence and nature of a double innervation to striated muscle. Physiologists generally believe that motor effects produced by the stimulation of the autonomic component are due to intramuscular vascular change. Boeke and his followers have adduced evidence pointing to an autonomic supply ending hýpolemmally on the muscle fibers. Hinsey among others has failed to repeat Boeke's work and has objected to Boeke's interpretation on technical grounds. The present investigation was carried out on the striated muscle of the swim bladder of the sea robin and gives a new aspect to the problem. Sections impregnated by the Bielschowsky technique showed that the muscle had a double motor innervation: a somatic type traceable from large medullated nerves entering the muscle substance to motor terminations and an autonomic type arising from ganglia within the muscle. It is possible to see a ganglion cell with its axon giving rise to a motor ending all within the one microscopic field. Therefore the innervation of the muscle is autonomic and somatic. If, as Hinsey believes, a single muscle fiber cannot be innervated from these two different sources, two different types of muscle fiber have to be postulated according to the source of innervation. Since there is no histologic reason for such a differentiation here, since each fiber has 6 or 7 simple endings, and since the ganglionic content of the muscle is small as compared with the somatic supply, an autonomically innervated fiber is believed to receive also a somatic innervation. Although this conjecture has not yet been confirmed by the direct observation of both types of ending on the one muscle fiber, the view held by Boeke appears to fit the facts of the innervation of this particular muscle.

* Zirkle, R. E., Aebersold, P. C., and Dempster, E. R.: *Am. J. Cancer*, 29, 556, 1937; Lawrence, J. H., Aebersold, P. C., and Lawrence, E. O.: *Occasional Publ. Am. Assn. Advancement of Science*, 4, 215, 1937.

A Consideration of Shock in the Normal and Completely Sympathectomized Dog. N. E. FREEMAN, A. E. SCHECTER, S. A. SHAFFER and H. E. HOLLING (Harrison Department of Surgical Research, University of Pennsylvania). A condition of shock was produced in normal dogs by means of hemorrhage. This condition was characterized by hemoconcentration, failure to respond to blood transfusion and characteristic pathologic changes in the tissues.

After total sympathectomy, even though the blood pressures were reduced to a lower level, for a longer period of time, shock was not produced. Dilution of the blood took place, there was prompt and beneficial reaction to blood transfusion and similar pathologic changes in the tissues did not occur.

The sympathectomized dogs, however, were unable to tolerate as large hemorrhages as the normal dogs. The blood pressure also fell to a lower level at an earlier period than in the normal dogs.

The difference in reaction of normal and sympathectomized dogs to hemorrhage was correlated with the peripheral blood flow. In the normal dog as the blood pressure was reduced by hemorrhage to 70 mm. of mercury the blood flow was reduced below 2 cc. per minute. In the sympathectomized dogs, at the same level of blood pressure, the blood flow was above 2 cc. per minute.

In 2 normal dogs which recovered, although the blood pressure was reduced to between 60 and 80 mm. of mercury, the blood flow continued above 2 cc. per minute. It was our impression that the absence of fear in these dogs predisposed them to recovery.

Vasoconstriction in the presence of hemorrhage, gives preferential treatment of blood supply to the vital centers, the heart and the brain. In the sympathectomized dog, such preference is lost. All the tissues of the body are accorded the same treatment. As long as the vital centers receive sufficient blood supply, all the tissues of the body probably receive an adequate amount of circulation and the condition of shock is prevented.

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